Do we currently see what we treat?

CartCasLab

http://www.cartcas.polimi.it/

POLITECNICO MILANO 1863

CNAO

Centro Nazionale di Adroterapia Oncologica

Chiara Paganelli, PhD

chiara.paganelli@polimi.it

Introduction - literature review

Scopus search (end of October 2021) – from 2019 to 2021
Keywords: ("motion" OR "motion modelling" OR "4D imaging" OR "4D" OR "external surrogate" OR "fiducial marker") AND ("particle therapy" OR "carbon ions" OR "proton therapy")

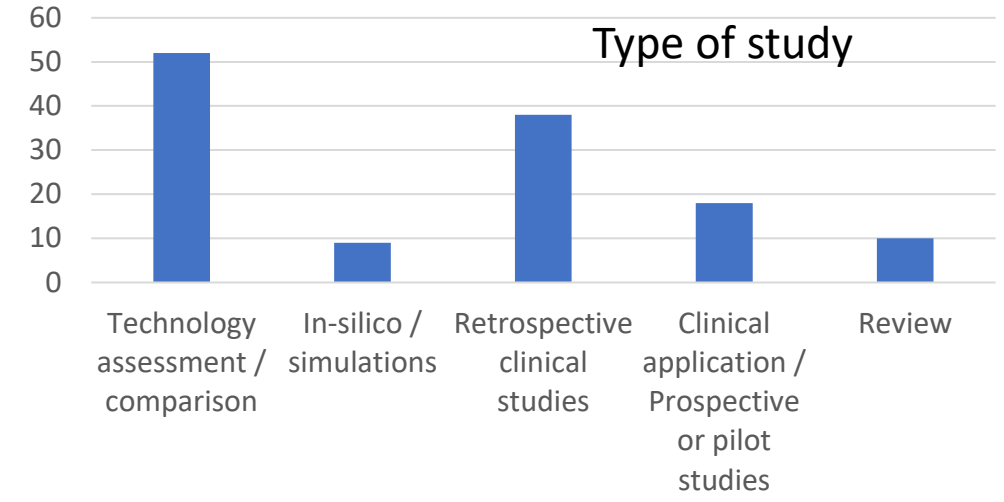
130 related documents found *<u>* May not be exhaustive</u>*

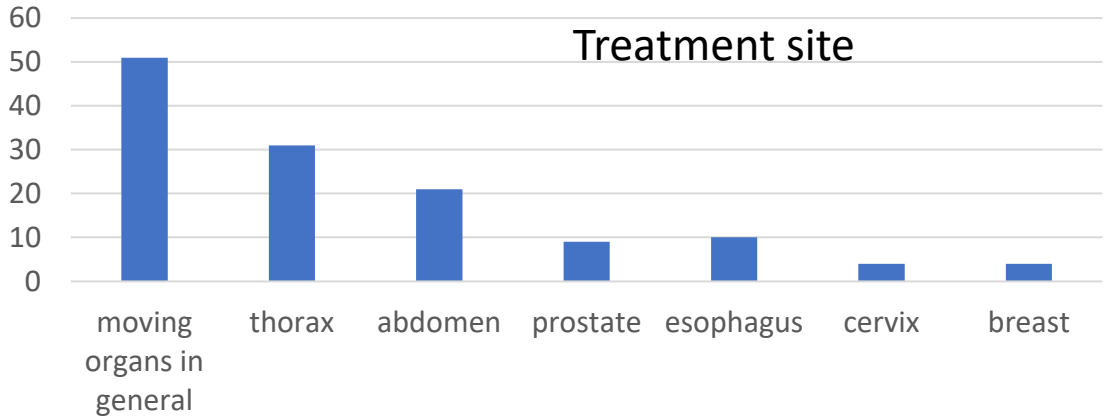
Documents categorized by:

- Type of study
  - Technology assessment / comparison
  - In-silico / simulations
  - Retrospective clinical studies
  - Clinical application / Prospective or pilot studies
  - Review
- Reference technology
- Treatment site

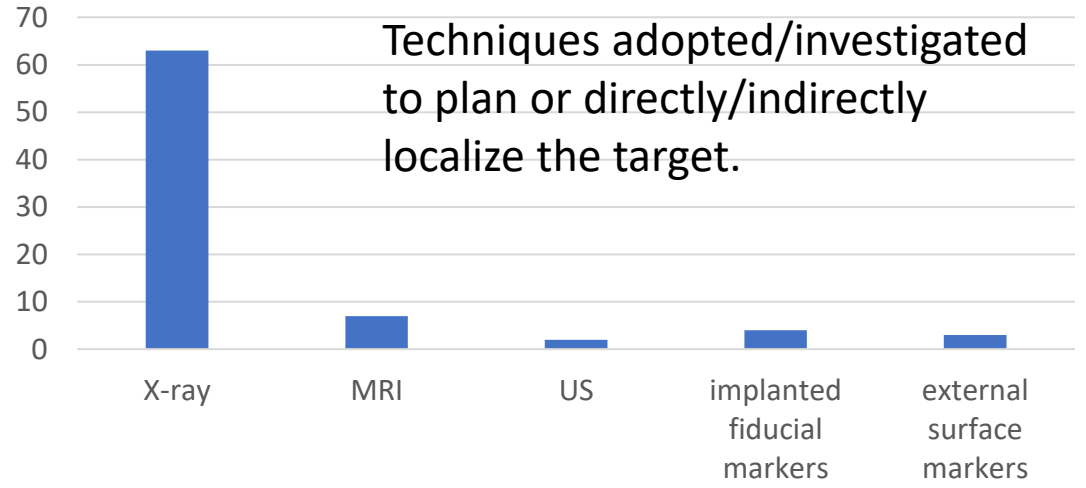
SC

Introduction - literature review





** May not be exhaustive*



Imaging adopted in most of the studies, with 4DCT as the standard to see and plan the treatment

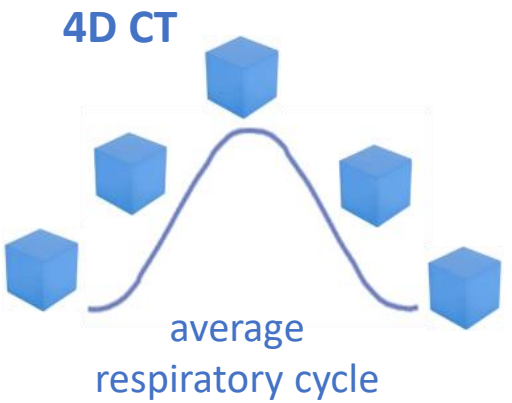
4DCT – the current standard technique

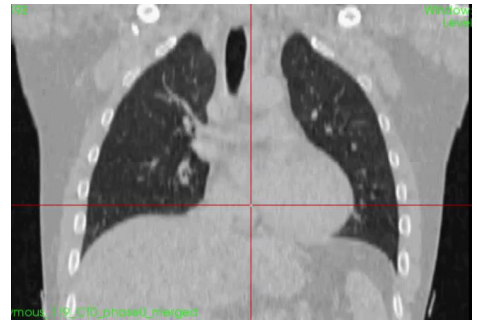
4DCT is THE standard technique for respiratory-correlated treatment planning / range of motion assessment in X-ray and PT.

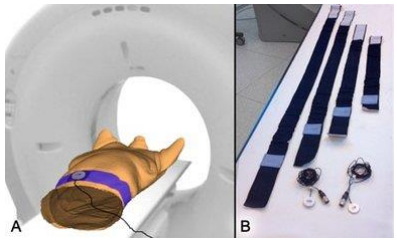
- It relies on anatomy correlation / reproducibility w.r.t. a 1-D signal provided by external surrogates over multiple breaths.

- External surrogates are essentially based on three technologies (optical, load cells, spirometric). The surrogate used for planning is then used for treatment.
  External surrogates tracking and position correlation with inner anatomy is state of the art for:
  - 4D imaging for treatment planning (X-ray and PT)
  - breath-hold irradiation
  - Respiratory gating
  - Tumor tracking (not yet implemented for PT)

- It performs a relatively low temporal resolution (6-12 respiratory phases, 0.8-0.4 sec per respiratory gate)







4DCT – the current standard technique

✓ Is the internal/external correlation robust enough?

Gierga et al. IJROBP, 2005

Internal/external motions are correlated, but it depends on:
- internal anatomo-pathological variations
- position of the external marker wrt the internal target

✓ Is a one-dimensional surrogate enough to describe the internal anatomy?

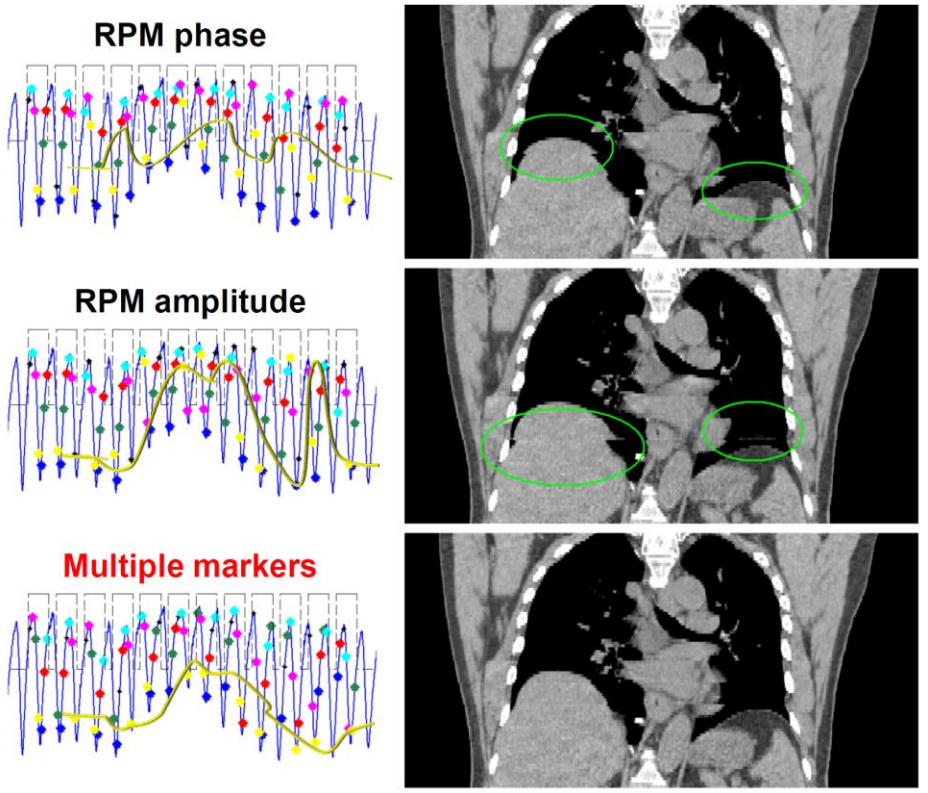
Gianoli et al. Med Phys, 2011

- multiple markers can improve 4DCT reconstruction (i.e. reduced motion artifacts)

✓ Is the temporal resolution enough to describe organ motion?

Riboldi et al. Lancet Oncol, 2012; Mori et al. Med Phys 2018

- **4D CT is not representative of each breathing cycle (intra-fraction variability) at each therapy fraction (inter-fraction variability)**



Gianoli et al. Med Phys, 2011

Introduction – Do we currently see what we treat?

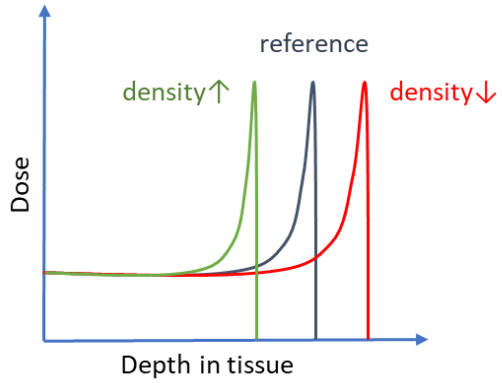
1. 4D CT is an average description of the respiratory motion
2. We rely on external surrogates during treatment for motion monitoring

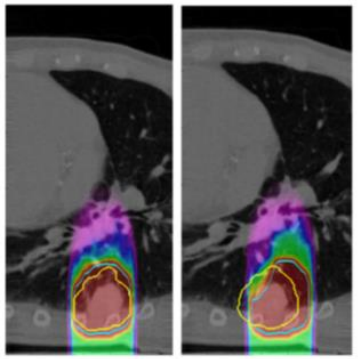
… not as well as we should

Organ motion

✓ tumor motion with respect to the planned position
→ geographical miss of the target

✓ variations of the tissue in the beam path
→ change of the radiological water equivalent path lenght (WEL)





Mori et al. Med Phys 2018

How can we see what we treat and improve inter- and intra-fraction motion management?

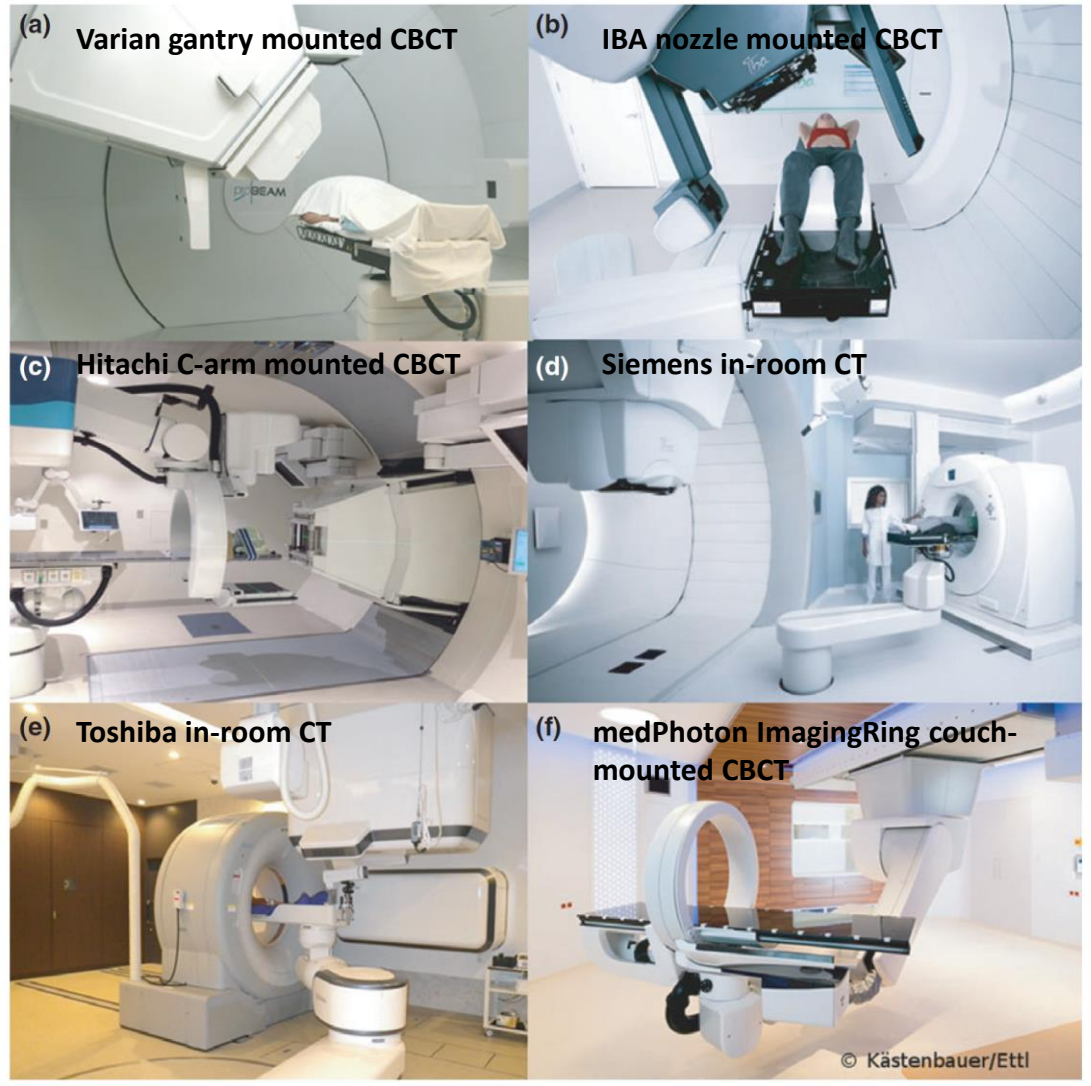
X-ray in-room imaging for inter-fraction motion management

- In-room orthogonal 2D X ray imaging (most of PT centres)
  -> Inadequate for monitoring the tissue changes (WEL) along the beam paths

- Volumetric imaging required
  Commercial in-room CT or CBCT
  In-house custom-made in-room CBCT system
  The CNAO case study

- Open the way to treatment plan adaptation (i.e. update the planning CT info on the basis of the in-room info) *[Landry et al. Med. Phys, 2015]*
  …Session of tomorrow on treatment adaptation by Stine Korreman @12:15

Landry et al. Med Phys, 2018

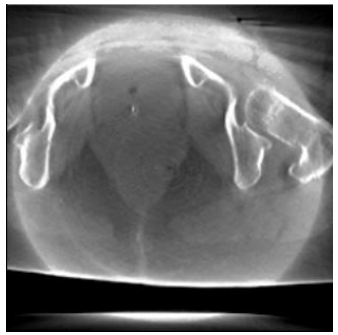


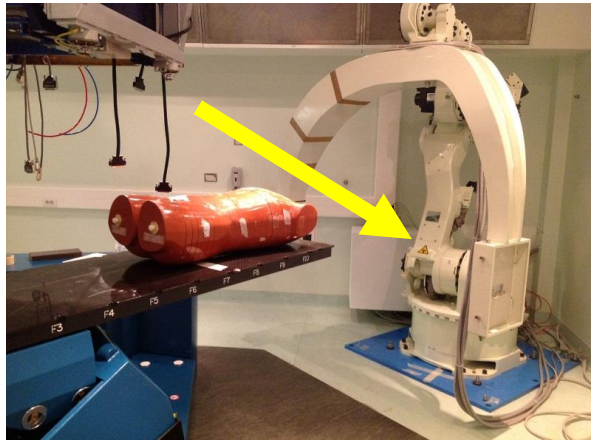
X-ray in-room imaging for inter-fraction motion management @CNAO

CURRENT STATE OF IMAGE GUIDANCE

- 6 DoF Patient Positioning System (PPS)
- IR optical tracking for setup and immobility verification

- Central room: custom C-arm for CBCT mounted on a 6 DoF robotic serial manipulator (Kawasaki ZX300)
  - ~600 projections over 220° ROM
  - 2D-3D based correction only
  - CBCT → Limited FOV and several artifacts





CNAO
Centro Nazionale di Adroterapia Oncologica

Advantages

- **Flexible and open system**

To improve

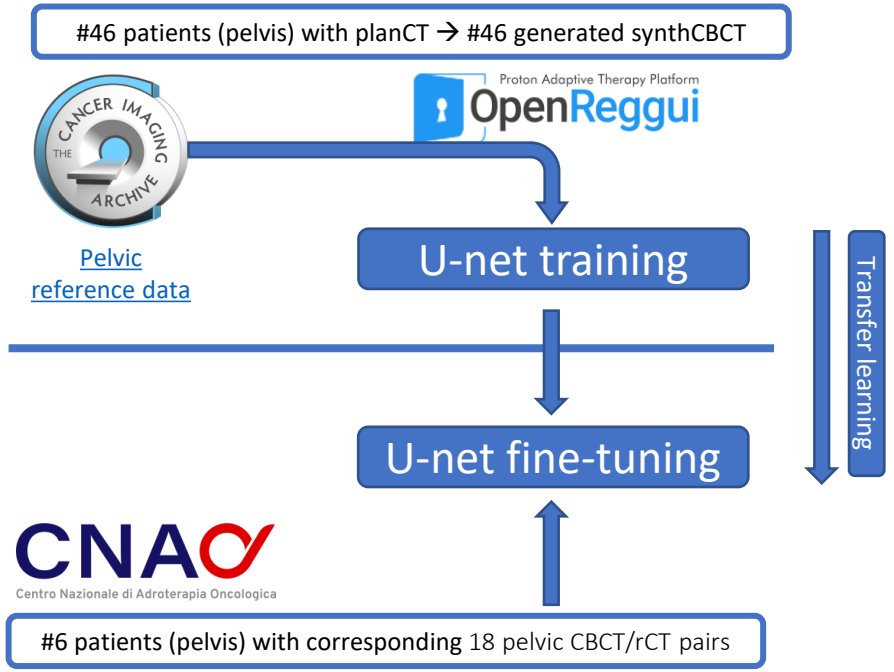
- **Augment Field of View**
- **Artifacts suppression**
- **HU calibration**

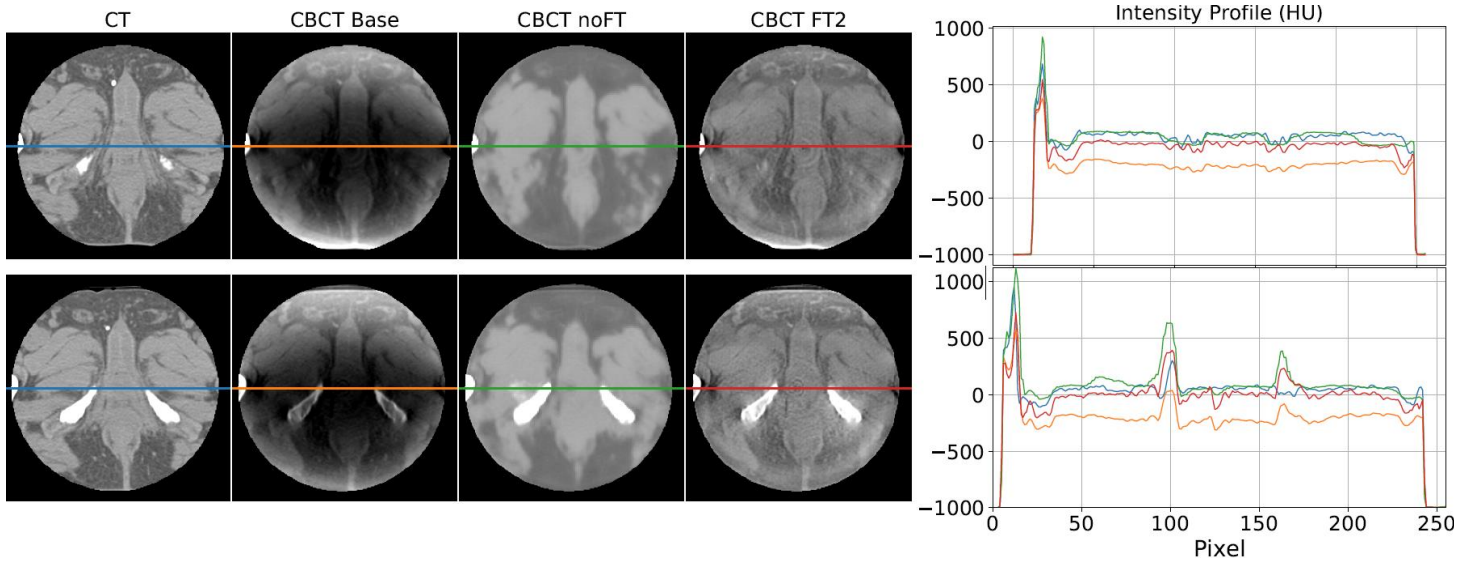
Courtesy of Belotti G.

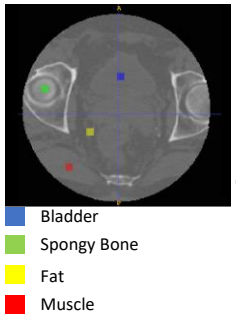
Fattori et al. Phys Med, 2015

X-ray in-room imaging for inter-fraction motion management @CNAO – image quality improvement

Improvement of what we see: using CT as prior to investigate cupping correction and HU calibration of CBCT of the pelvis







Accuracy

Model	Bladder	Spongy Bone	Muscle	Fat	All
Base (HU)	213.06 (47.19)	340.79 (66.06)	249.36 (20.53)	199.27 (39.46)	161.37 (162.54)
FT_2 (HU)	23.11 (20.87)	83.75 (55.41)	42.48 (28.83)	29.54 (19.40)	49.41 (66.70)
Improvement	89%	75%	83%	85%	70%

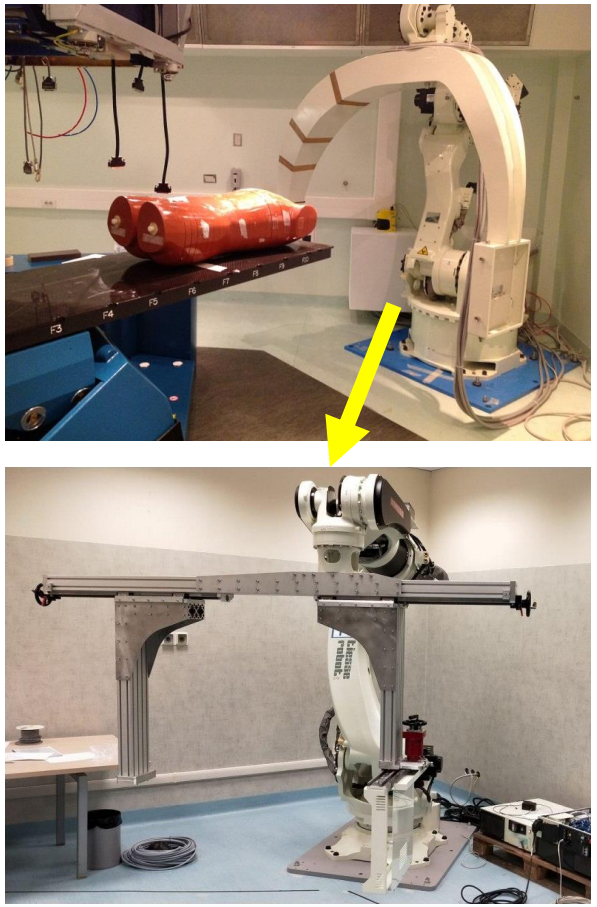
X-ray in-room imaging for inter-fraction motion management @CNAO – HW upgrade

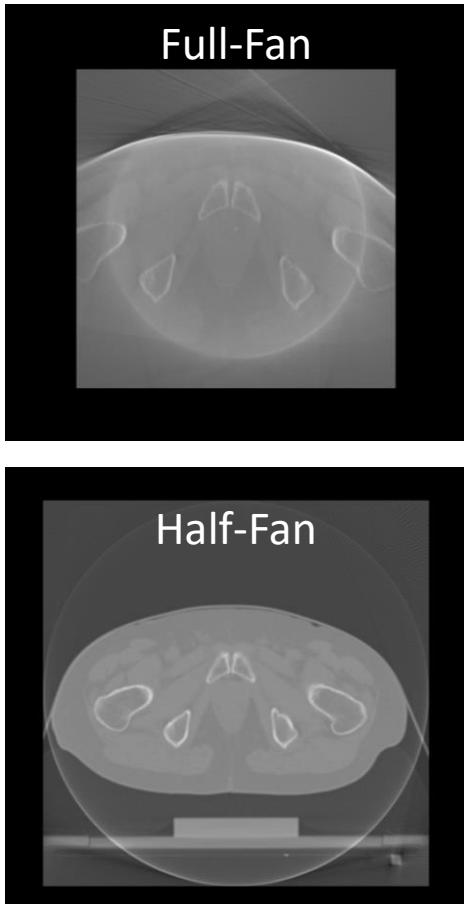
CURRENT <u>DEVELOPEMENT</u>

- 6 DoF Patient Positioning System (PPS)
- IR optical tracking for setup and immobility verification

- Lateral room: custom C-arm for CBCT mounted on a **7** DoF robotic serial manipulator (Kawasaki **BX300L**)
  - ~600 projections over 220° ROM
  - CBCT based 3D/3D registration
  - **Moving Flat Panel Detector**
  - **Custom collimator**
  - **Wider CBCT FOV (Half Fan mode)**

…WORK IN PROGRESS…

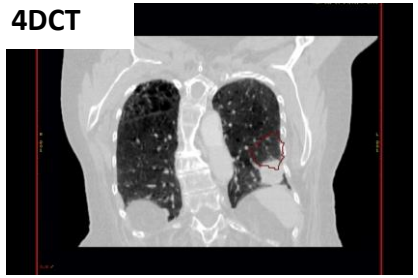




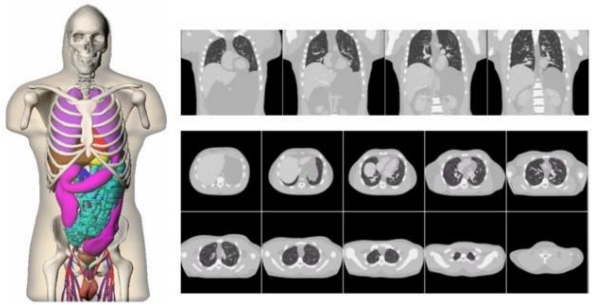
Courtesy of Belotti G.

X-ray in-room imaging @CNAO – 4DCBCT

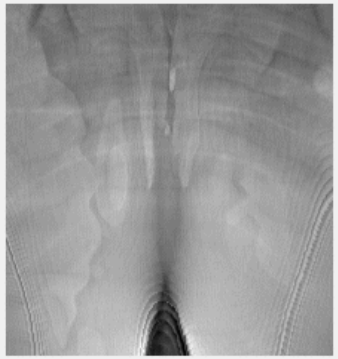
4DCT

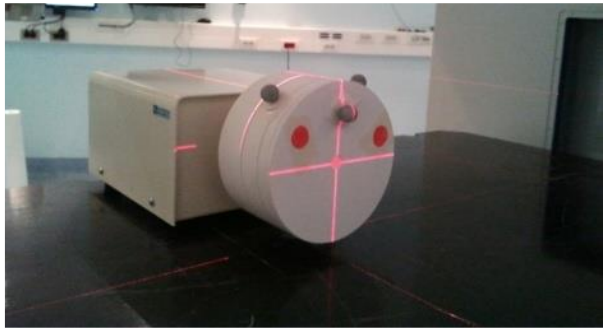


More precisely, an in-room volume depicting the end-exhale anatomy would be ideally required, which in turn would require the acquisition of a **time-resolved CBCT** [*Meschini et al. Med Phys 2017*]



4D extended cardiac-torso (XCAT) phantom



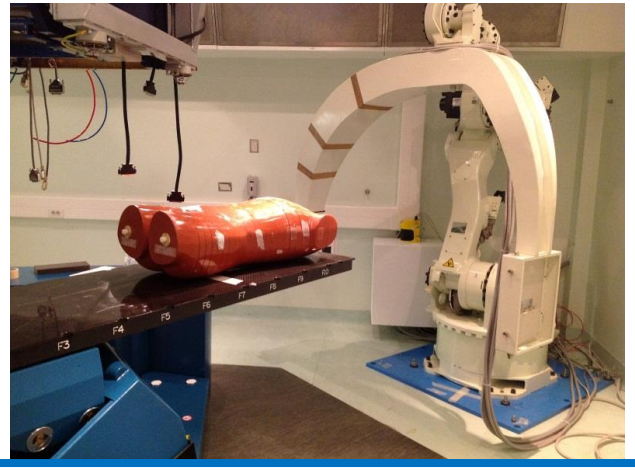


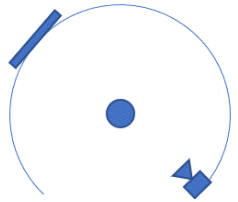
ANZAI Synchronized phantom

CNAO
Centro Nazionale di Adroterapia Oncologica

Work in progress

Custom CBCT (@CNAO) [Fattori et al. 2015]

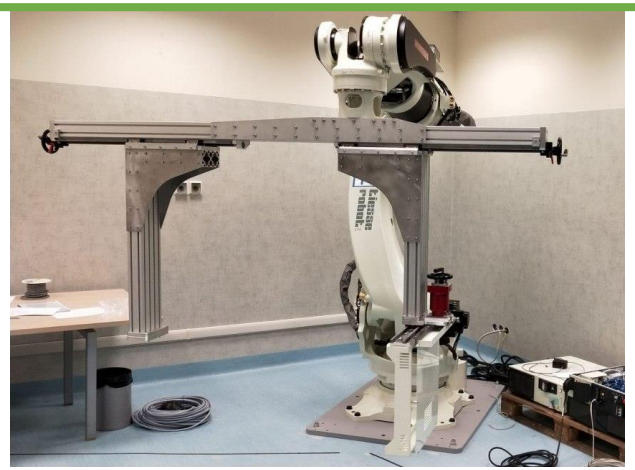


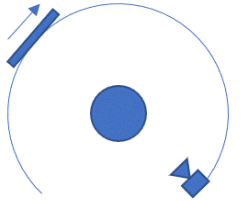


Repeated Full Fan acquisitions

Future work

Custom CBCT Room1 Upgrade (@CNAO)





Half Fan acquisition

Courtesy of Belotti G.

Belotti G. et al. POSTER @4D Treatment Workshop

Direct and indirect target localization for intra-fraction motion management

Fluoroscopy
[Shirato 1999]

(+) Direct target localization
(-) More imaging dose

Internal/external correlation models
[Schweikard 2000]

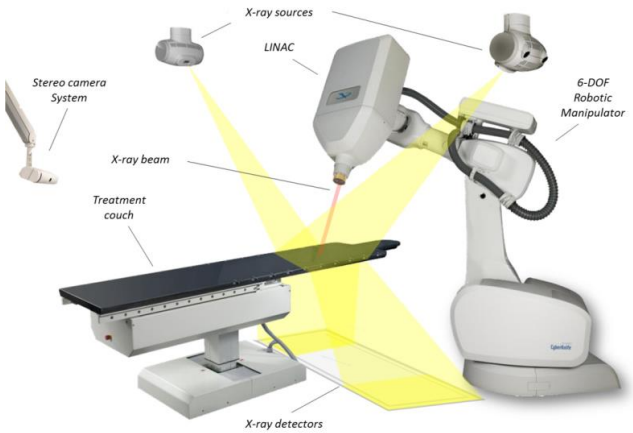
(+) Less imaging dose
(-) Indirect target position estimation

Clinical application for tumour tracking in X-ray RT

- Not yet implemented in PT, where the current standard for treatment of moving organs is gating.
- Tracking with particle beams requires lateral beam adjustments and energy adaption for compensation of range changes resulting from motion induced density variations.
- Thus, **tracking can only be effective if time-resolved 3D information on the tumor location is known at all times.**

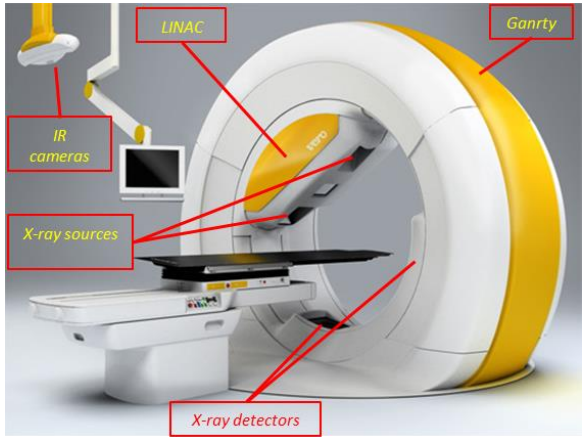
Mori et al. Med Phys, 2018

CyberKnife Synchrony®



[Kilby 2010]

VERO™ System

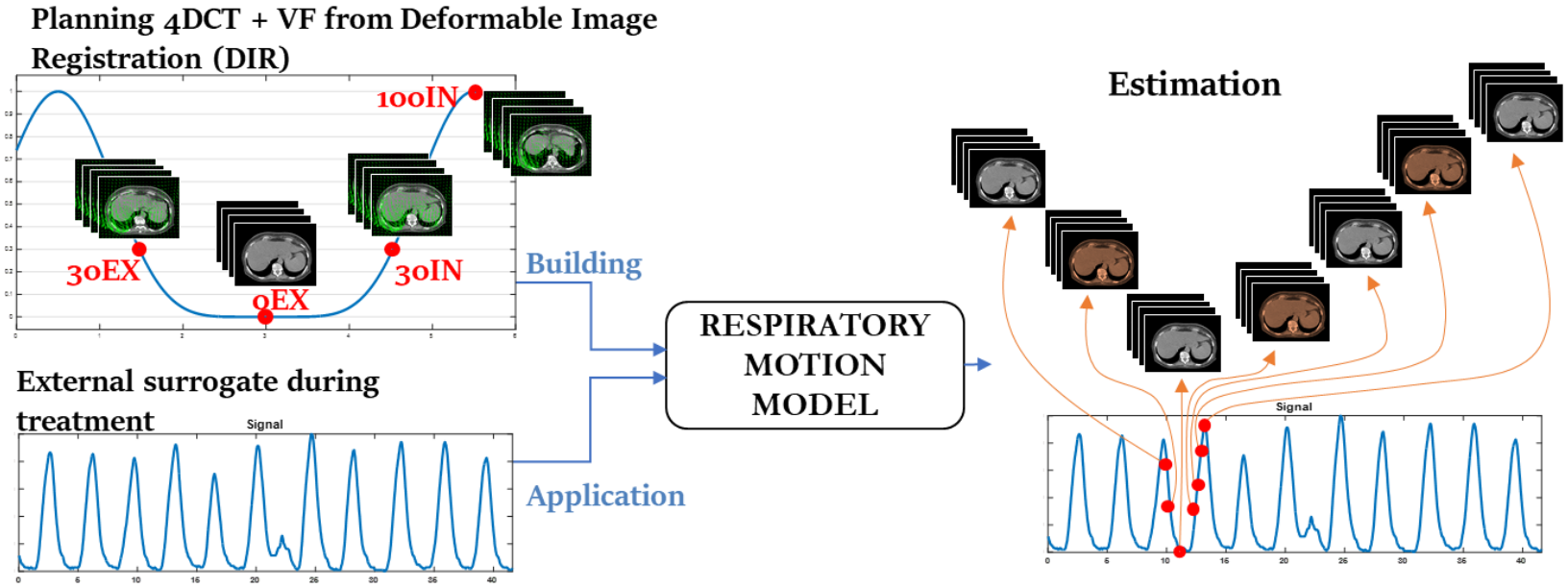


[Depuydt 2013]

Motion modelling

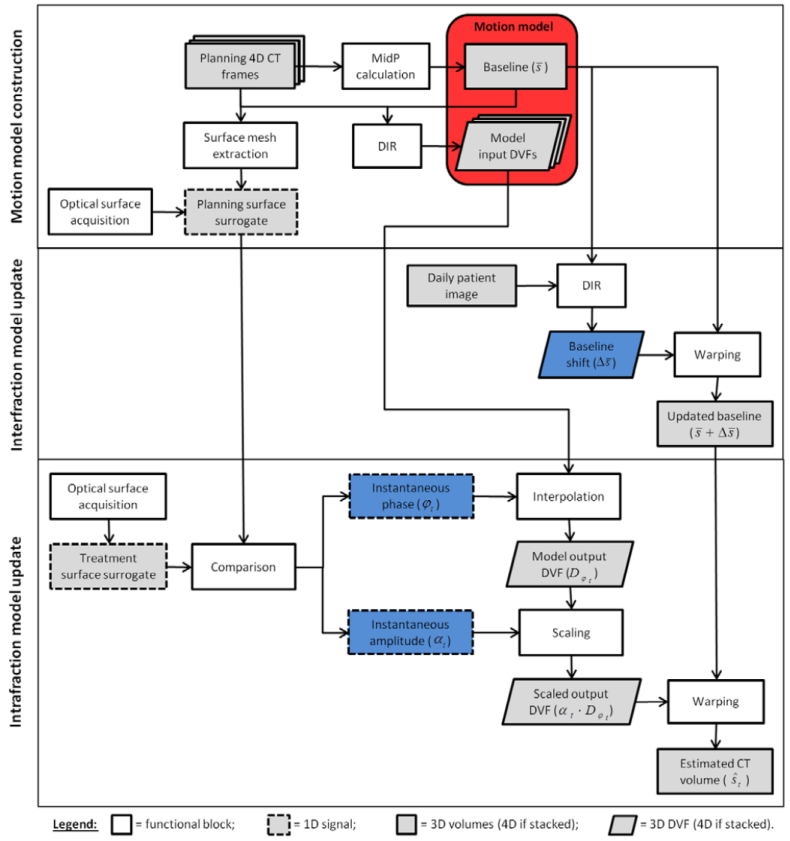
Motion modelling techniques can be adopted to estimate respiratory phases not seen in the acquired planning 4DCT (or 4D imaging in general)

- Local motion modelling (estimation of few points, e.g. tumor centroid)
- **Global motion modelling (estimation of the whole anatomy – complete information on density and WEL variations required for particle beam range adaptation)**



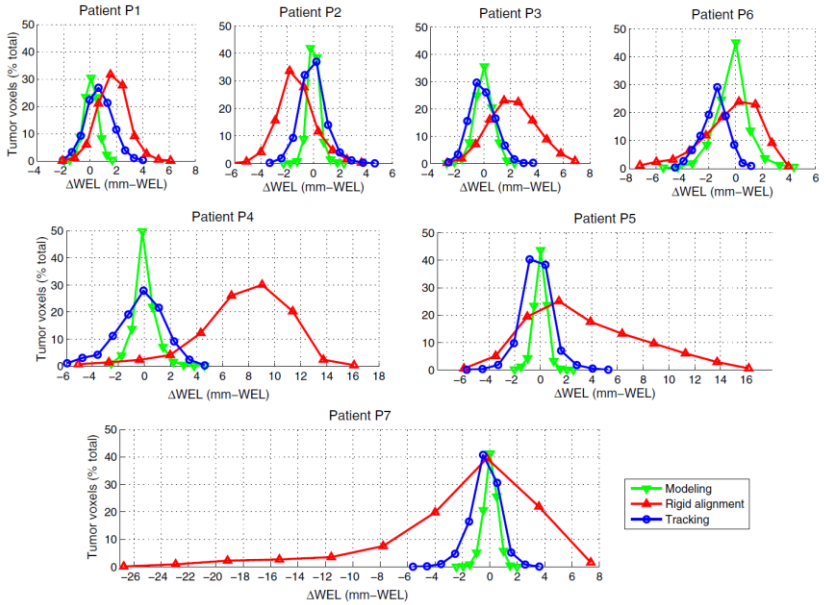
Motion modelling in PT

7 lung pts with two 4DCT (one for building the model, the other for testing)

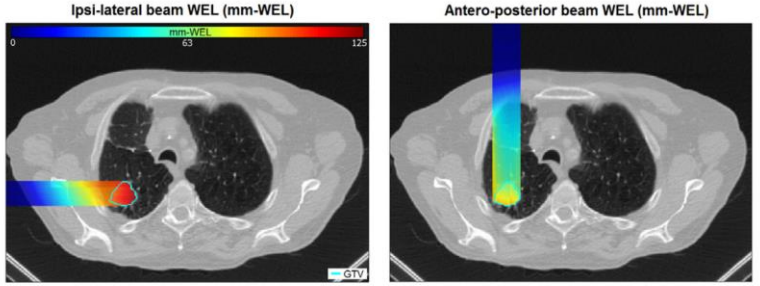


Modeling: model accuracy
Rigid alignment: current clinical procedure for setup correction
Tracking: ground truth (4DCT1 vs. 4DCT2)

WEL variations



Geometric error < 1.3mm
ΔWEL median values < 1.9 mm-WEL
[in accordance with *Kumagai et al 2009*]

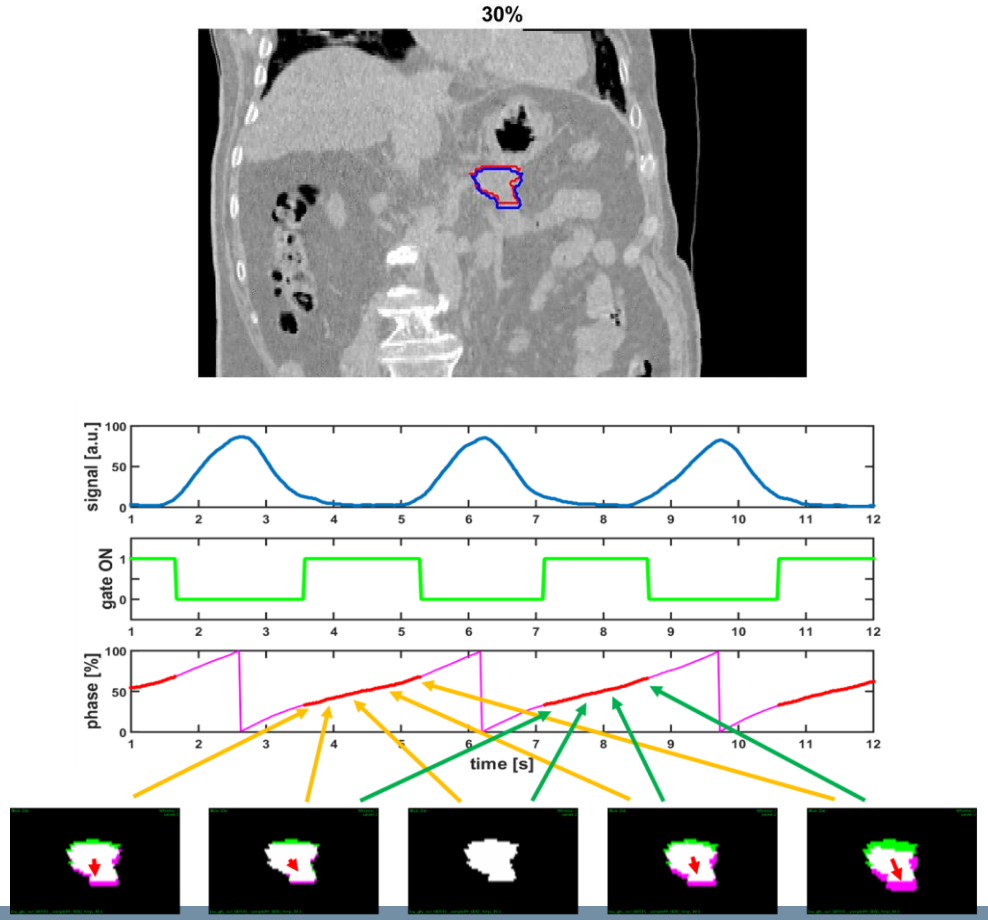


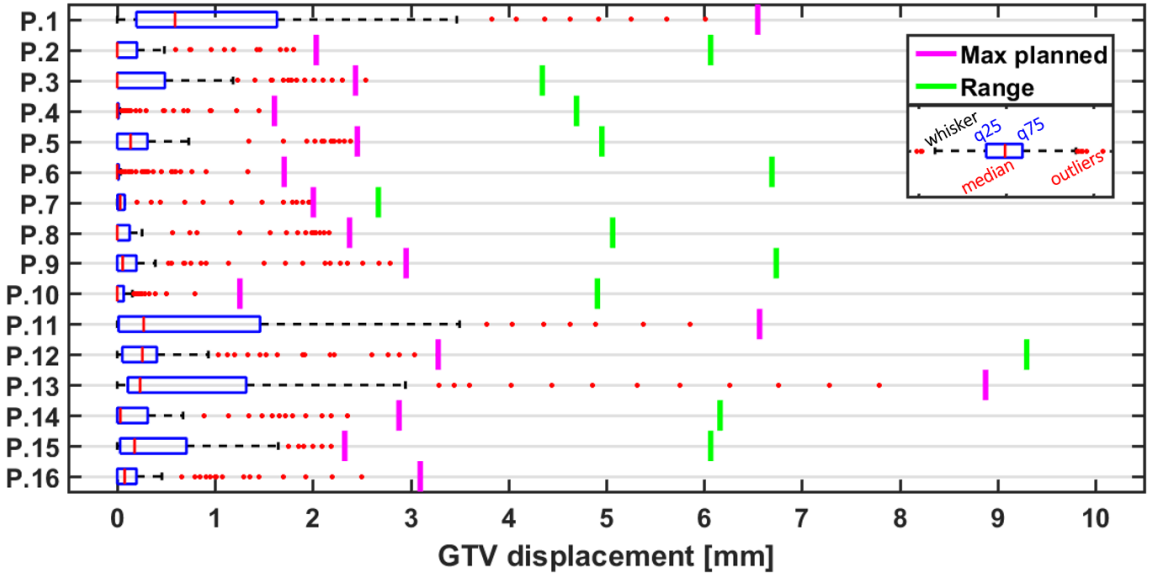
V Dynamic localization of all anatomical structures scanned in the planning CT.
V Complete information on density and WEL variations required for particle beam range adaptation

Fassi et al. PMB 2015

Motion modelling in PT

Residual tumor motion quantification in gated treatments





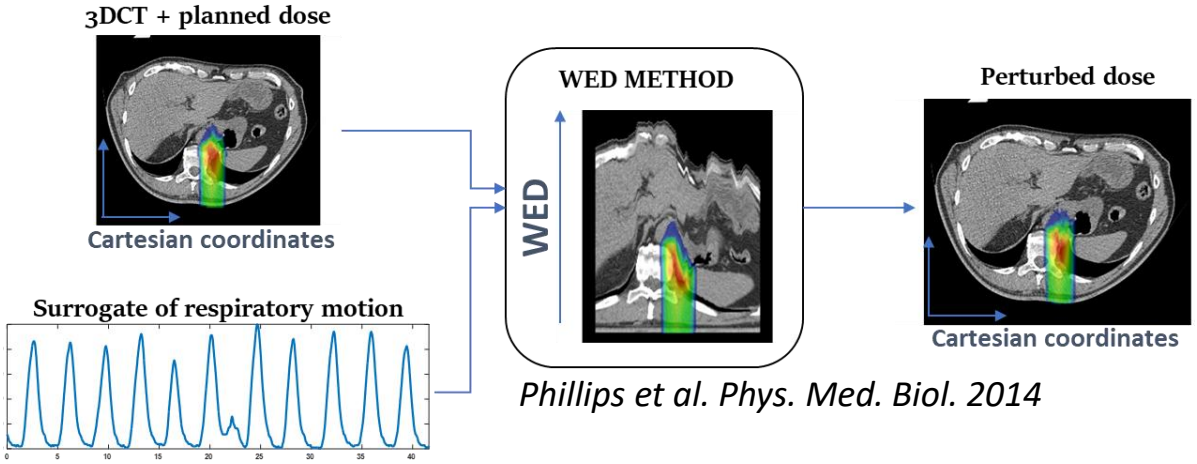
Average motion over 16 patients: 0.32 mm (standard deviation = 0.65 mm), which corresponds to 4% of the average GTV range of motion (7.4 ± 4.2 mm) and 10% of maximum planned motion (3.3 ± 2.1 mm).

V effectiveness of the gating procedure at CNAO

Meschini et al. Phys Med 2017

Dose variation models: estimation of physical dose variations in gated carbon ion treatments

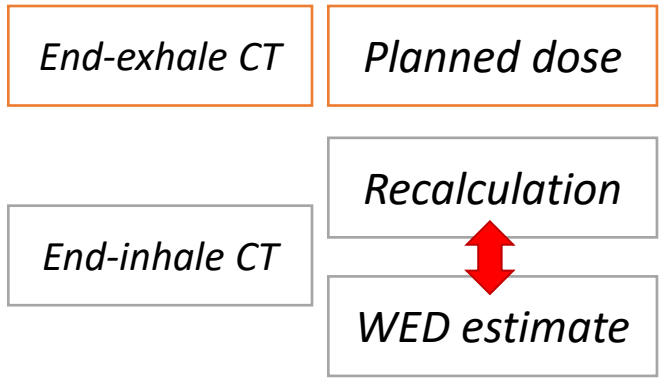
Water Equivalent Depth (WED) space



Phillips et al. Phys. Med. Biol. 2014

Aim: evaluate the validity and limitation of the WED method for the estimation of dosimetric variations induced by respiratory motion in abdominal sites.

Data: 4DCT of 12 gating patients treated at CNAO.



Median (interquartile range) over all patients.

Structure		Motion	Error
Tumor	$\Delta D5$	0% (1%)	0% (1%)
	$\Delta D95$	-20% (60%)	1% (6%)
OARs	$\Delta D2$	2% (36%)	4% (12%)
	$\Delta D50$	0% (11%)	0% (2%)

Clinical tolerance 5%.

✓ The method can estimate dose variations in case of intra-fractional motion

✗ Limitations: deformation not modeled, missing RBE information

Courtesy of Meschini G.

Meschini et al. Med Phys 2019

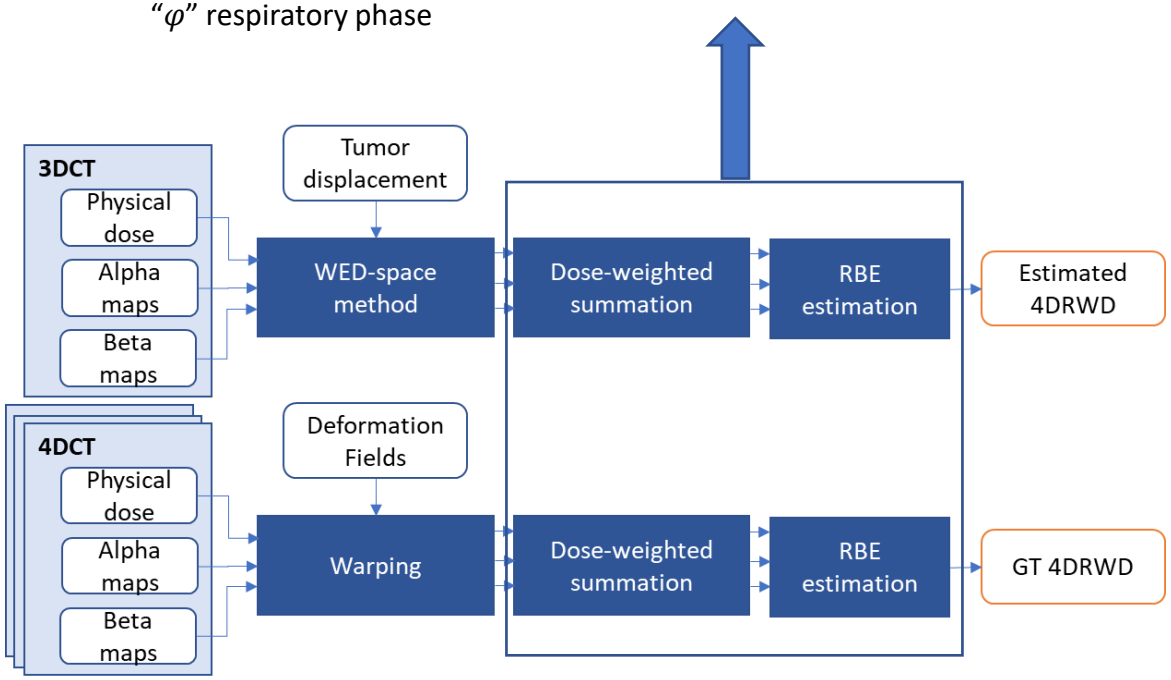
Dose variation models: estimation of RBE dose variations in gated carbon ion treatments

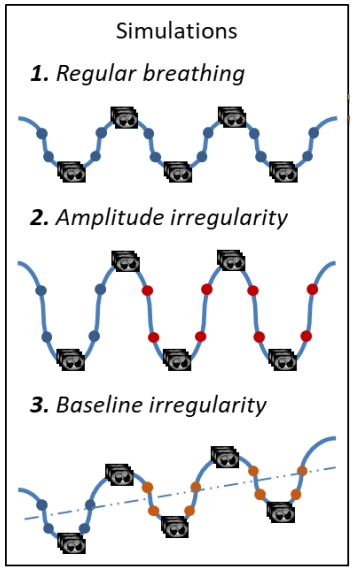
$$D = \sum_{\varphi}^{N} D_{\varphi} \qquad \alpha_P = {\sum D_{\varphi}\alpha_{P\varphi}}/{D}$$

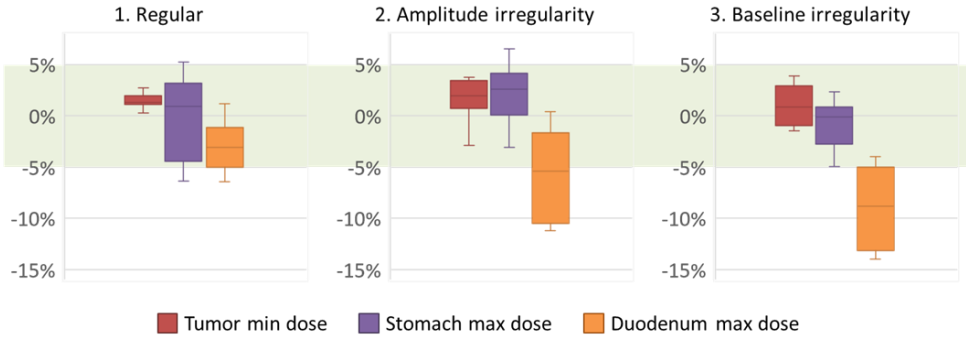
fixed α_x and β_x $\qquad \sqrt{\beta_P} = {\sum D_{\varphi}\sqrt{\beta_{P\varphi}}}/{D}$

$$RBE = \frac{-\alpha_x + \sqrt{\alpha_x^2 + 4d_P\beta_x(\alpha_P + \beta_P d_P)}}{2d_P\beta_x}$$

"x" photon, "p" particle,
"φ" respiratory phase







V Proper accuracy when compared to deformable image registration-based 4D dose calculation.

X Accuracy decreases as a function of increasing soft tissue deformation

Meschini et al. Med Phys 2020

Image-based motion modelling and dose variation models

Image-based motion models

- V able to estimate unseen respiratory phases
- V can be used to support treatment planning optimization, planning robustness evaluation or dose verification
- X still refer to a planning 4DCT -> not able to compensate for intra-treatment conditions that are different from treatment planning
- X depend on DIR accuracy *[Brock et al. Med Phys 2018, Paganelli et al. Med Phys 2018]*
- X still rely on a mono-dimensional external surrogate to estimate unseen respiratory phases
- X not yet implemented in real-time for tracking

Dose variation models

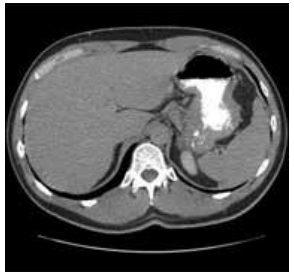
- V able to estimate unseen respiratory phases
- V no need of a 4D imaging (but just 3D) and fast to be used
- V can be used to support treatment planning optimization, planning robustness evaluation or dose verification
- X still rely on a mono-dimensional external surrogate to estimate unseen respiratory phases
- X not yet implemented in real-time for tracking
- X do not include deformations

Still not seeing what we are treating, but just estimating…

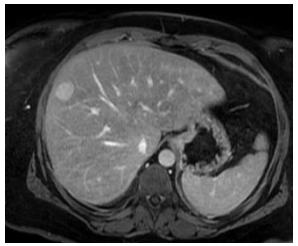
MRI-guidance

Why Magnetic Resonance Imaging?

- absence of ionizing radiation
- better soft tissue contrast
- lower acquisition time in dynamic modality



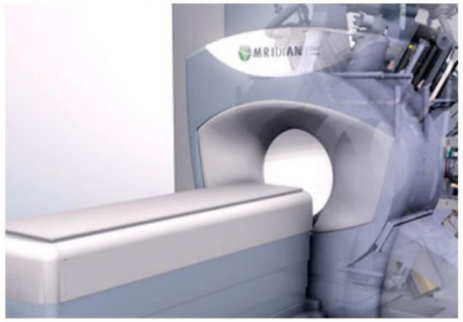
Liver CT



Liver MRI

Elekta-Unity MRI-linac

Viewray - MRIdian

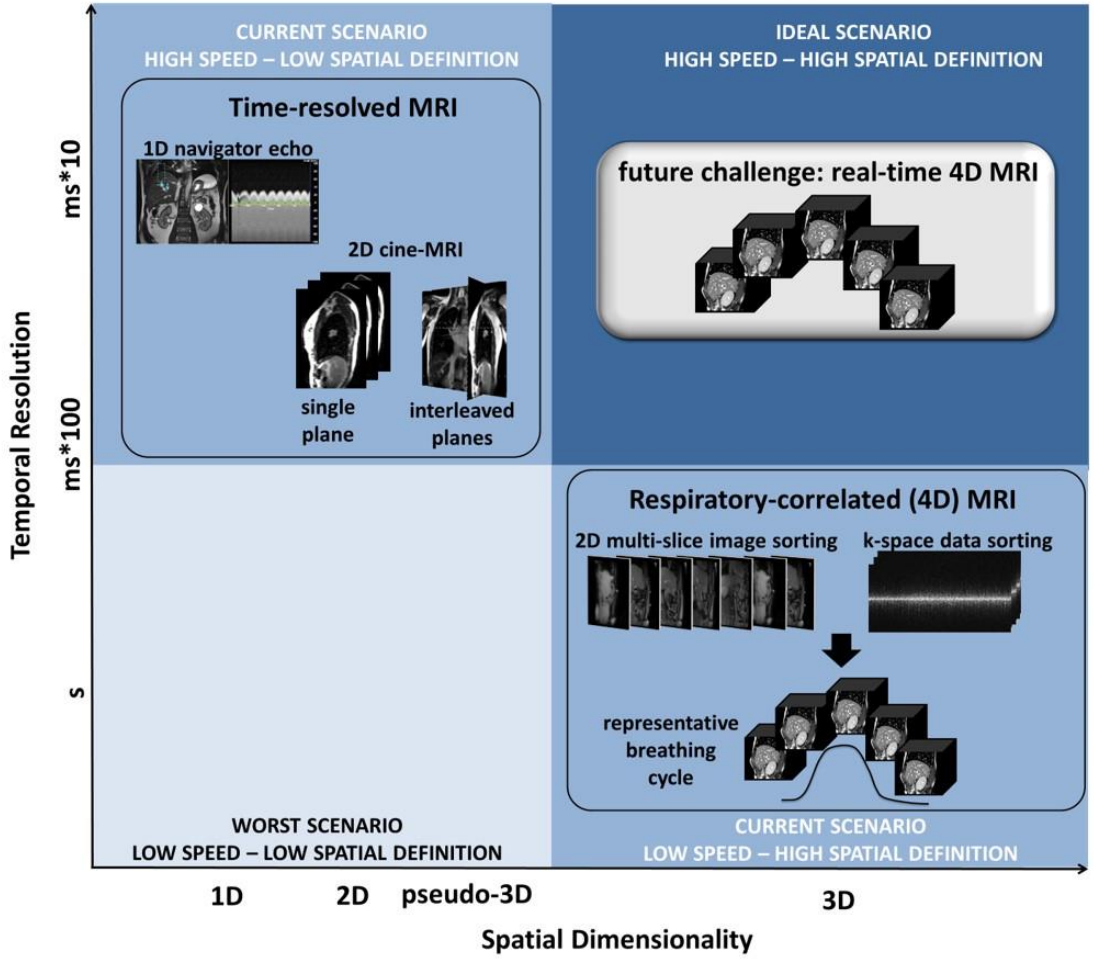


Commercial MRI-linac systems in X-ray RT
[Raaymakers et al. PMB 2017, https://viewray.com/]

Not yet present in PT, but with feasibility studies for proton therapy *[Hoffmann et al. Rad Oncol, 2020]*

MRI-guided PT expected to improve treatment outcome for liver tumors wrt CBCT-guided PT *[Moteabbet et al. PMB 2021]*

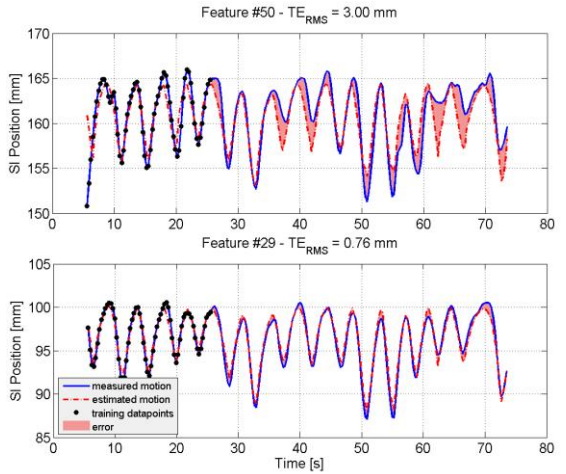
MRI-guidance for organ motion management

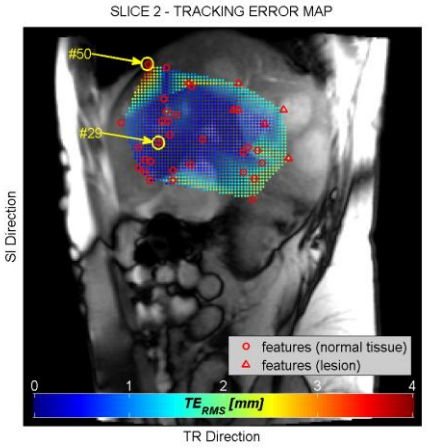


2D cine-MRI

State-of-the-art imaging for intra-fraction motion mangement in MRI-linacs

- High temporal resolution (150 ÷ 400 ms)
- Different plane orientations



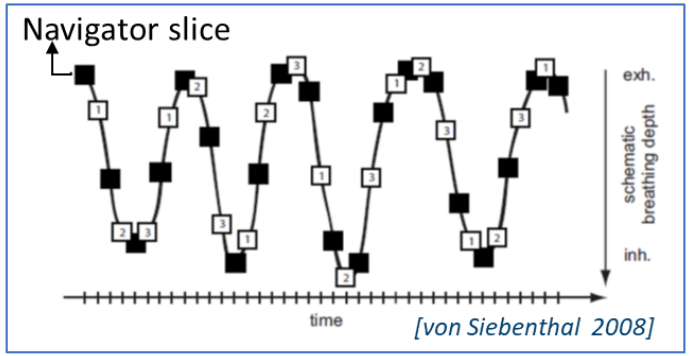


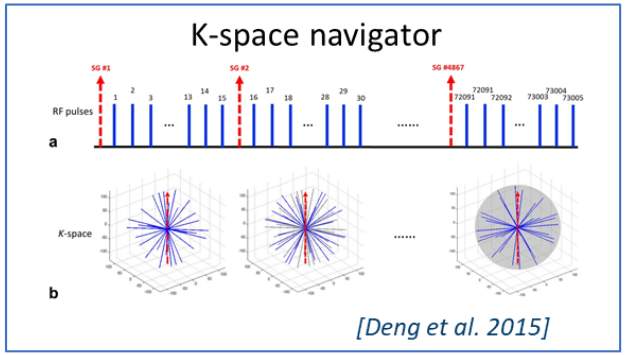
The gain of MRI guidance compared to surrogate-based motion tracking was larger than 30% in 50% of the subjects when considering a 1.5-mm tracking error tolerance.
[Paganelli et al. IJROBP 2015]

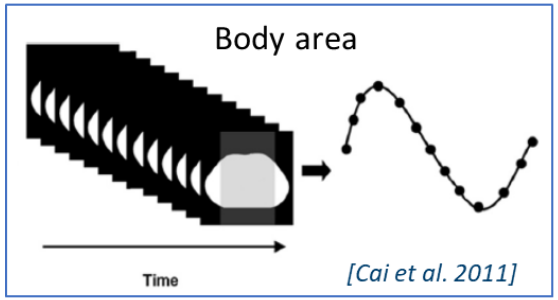
Paganelli et al. PMB, 2018
Kurz et al. Rad Oncol, 2020

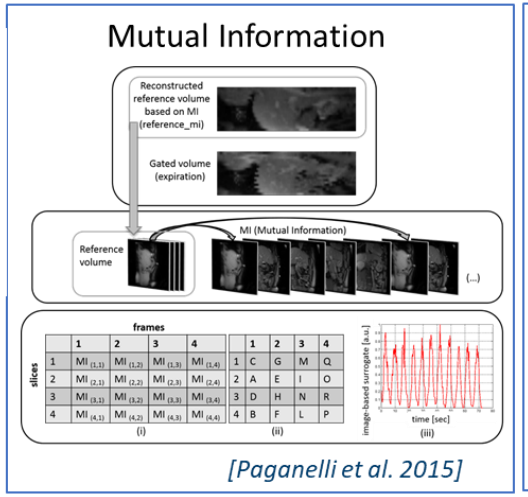
MRI-guidance: respiratory-correlated 4DMRI

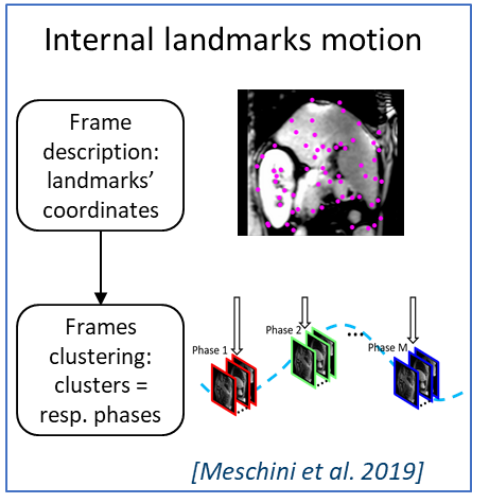
- Real time 3D *[Blackall et al. 2006]*: poor spatio-temporal resolution
- Prospective sorting (i.e. acquisition @ specific phases) *[Tokuda et al. 2008]*: quality limited by triggering efficiency
- Retrospecive sorting (i.e. continous multi-slice 2D acquisition and subsequent sorting):
  - External surrogates: poorer correlation with internal motion → sorting artifacts
  - Internal/image-based surrogates











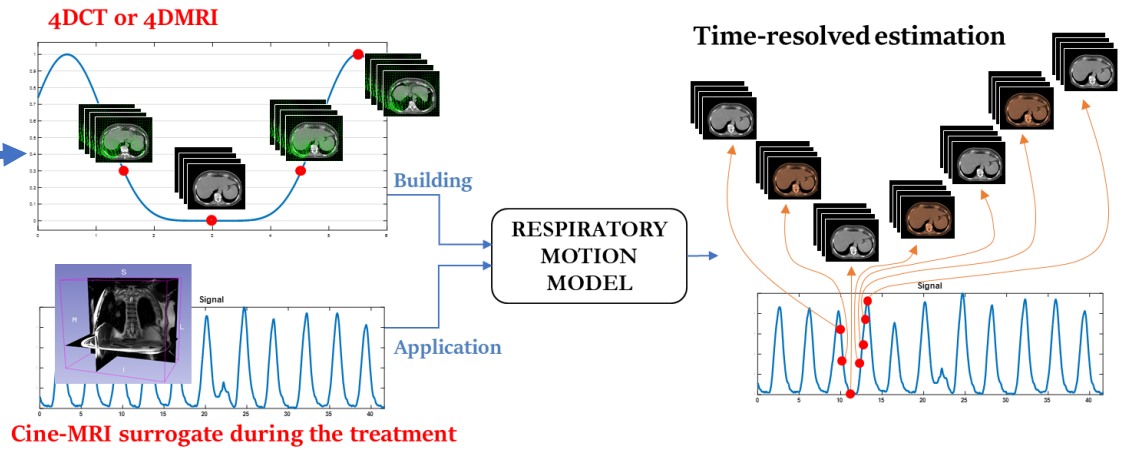
Paganelli et al. Med Phys 2015; Meschini, Paganelli et al. Phys Med 2019; Paganelli et al. Med Phys 2018

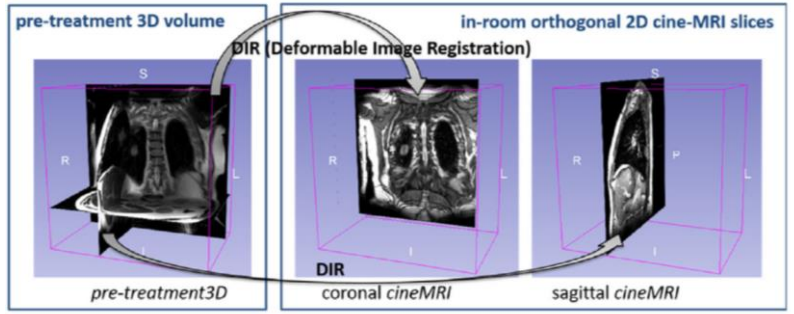
MRI-guidance: time-resolved imaging

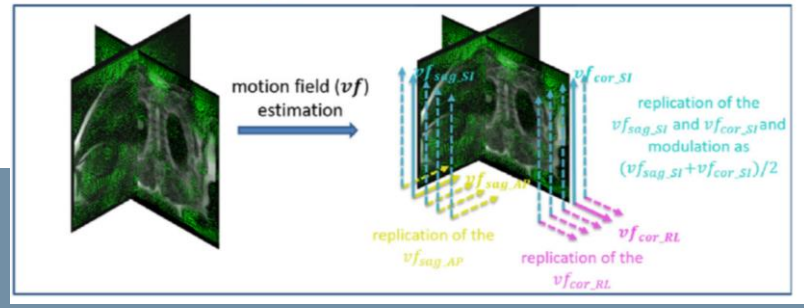
- ✗ 4DMRI still an average description
- ✗ cineMRI lacks 3D information

Fast/simple Global motion models solutions

Fayad model *[Fayad et al. IEEE 2012]*	Surrogate: Tumor position OR Diaphragm position
ROI-based model *[Garau, … Paganelli PMB 2019]*	Surrogates: Max filtered 2DVF ROI 1 (Tumor) & Max filtered 2DVF ROI 2 (Diaphragm)
Stemkens model *[Stemkens et al. PMB 2016]*	$\boldsymbol{w_{opt}} = \underset{w}{\operatorname{argmax}}\, Sim\,(I_{2D}, I_{3D,w})$
Propagation *[Paganelli et al. J Med Imaging Radiat Oncol. 2018]*	Propagation of the 2D VF
OOPM *[Seregni et al. Rad Oncol. 2017]*	In-plane motion from cineMRI Out-of-plane motion from 4DMRI



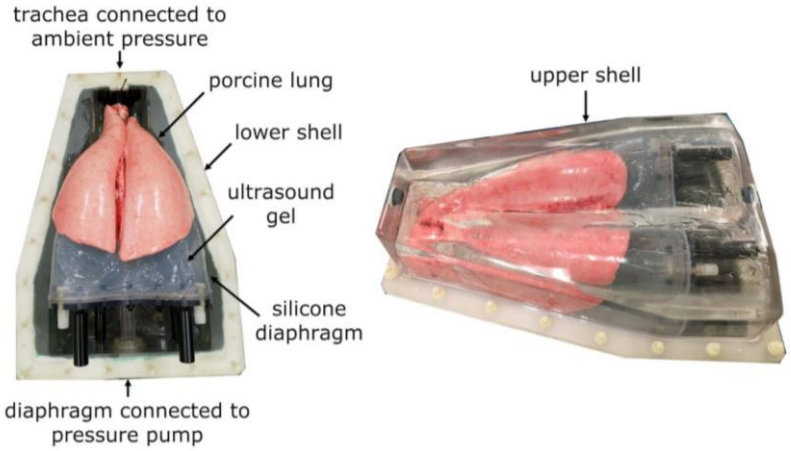


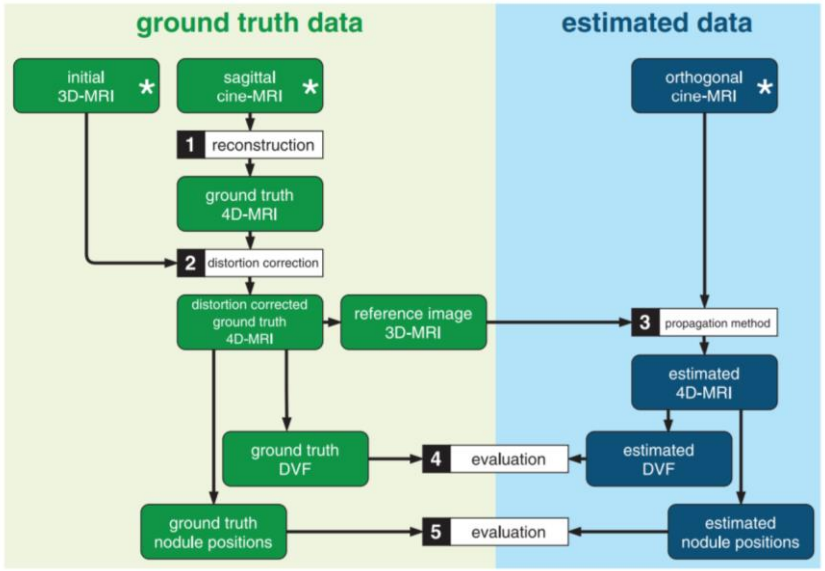


Paganelli et al. PMB, 2019

MRI-guidance: experimental validation

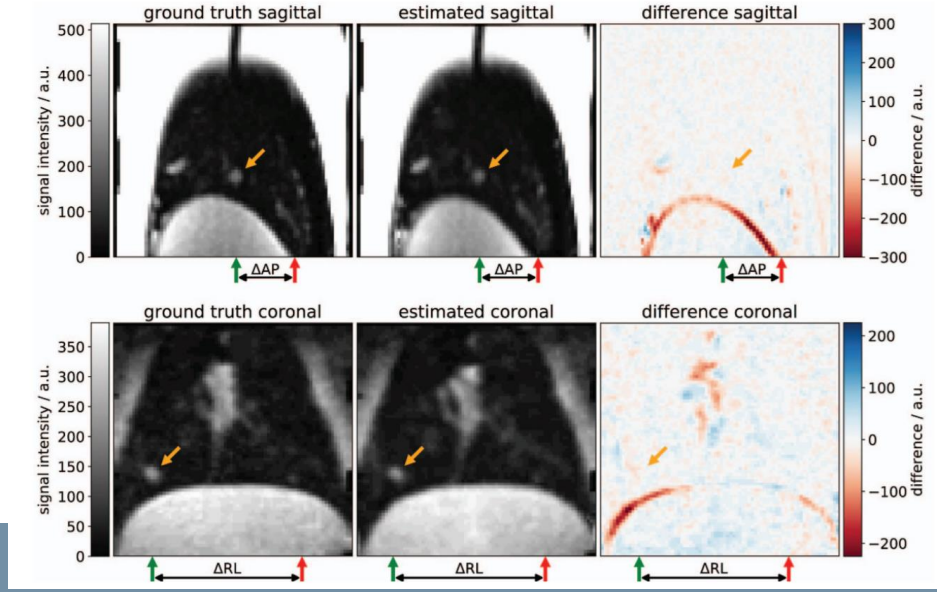
Experimental validation of the Propagation method by Paganelli et al. 2018





- Measurements performed using the MR scanner unit of a research version of the commercial MRIdian MR-Linac (ViewRay Inc., Oakwood Village, Ohio, USA) with a magnetic field strength of 0.35 T
  (5 mm slice thickness; 3.5 × 3.5 mm^2 in-plane resolution)
- 8 acquisitions with 3 lung pig phantoms, variable motion and frequency

- Median error (95th prc) of 2.3 (5.7)mm for all respiratory phases



Rabe, Paganelli et al. PMB, 2021

MRI-guidance: 4DMRI @ CNAO

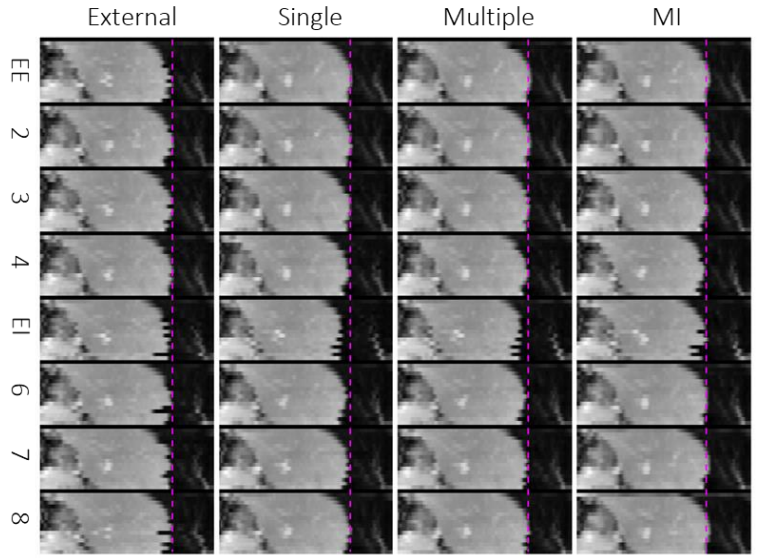
CNAO
Centro Nazionale di Adroterapia Oncologica

Dataset

Acquisition protocol approved by Ethical Committee @CNAO (thoraco-abdominal site)

Up to 15 patients treated with CIRT.

- 4DCT/3DCT
- 4DMRI reconstruction performed with multiple internal points [*Meschini et al. Phys Med. 2019*]: similar image quality of MI but able to describe a higher range of motion
- 2D orthogonal cineMRI

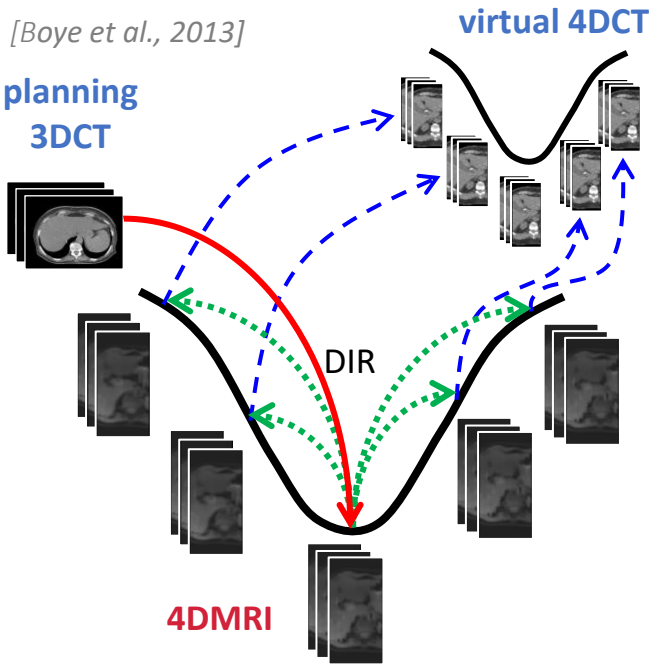


Meschini, Paganelli et al. Phys Med. 2019

MRI-guidance @ CNAO: virtual 4DCT in CIRT

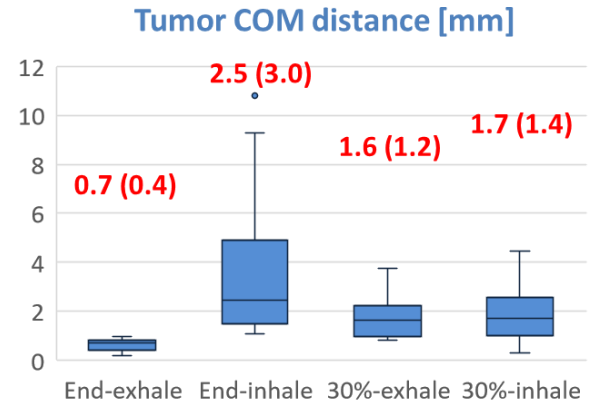
virtual 4DCT from 4DMRI

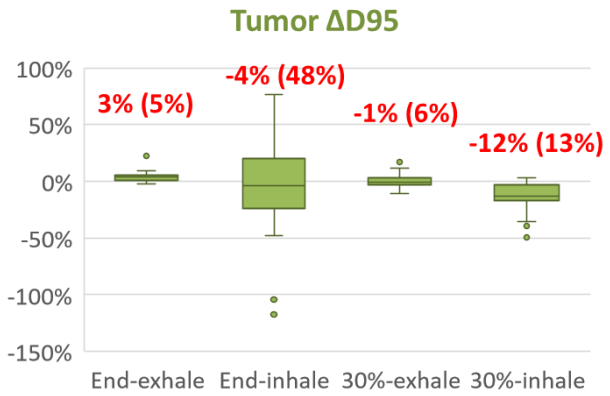
[Boye et al., 2013]

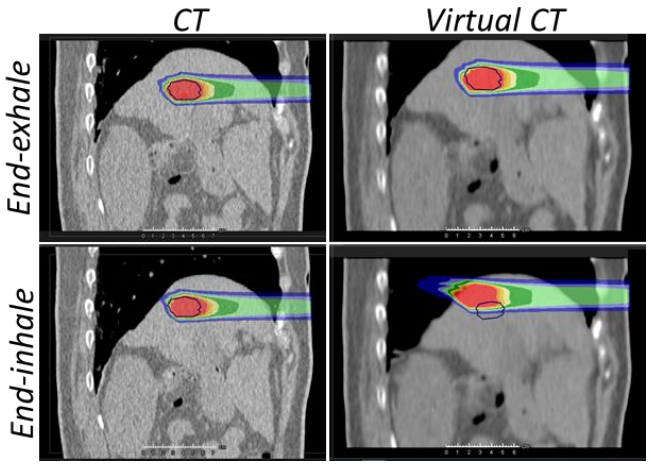


Phantom validation: available ground truth, error <1.8 mm for all phases

Dataset: 8 liver/pancreas patients (18 MRI) treated with CIRT, 4DCT + 4DMRI







- Good agreement at end-exhale → alternative to verification 4DCT
- Motion variability at different phases → valuable for intra-fraction motion evaluation

V Application to patient cases treated with CIRT @CNAO

~ DIR accuracy

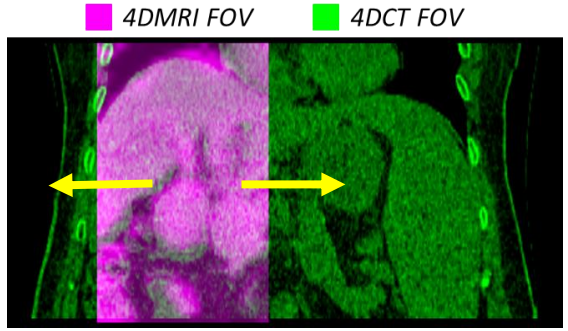
X Limited FOV (single beam)

Courtesy of Meschini G.

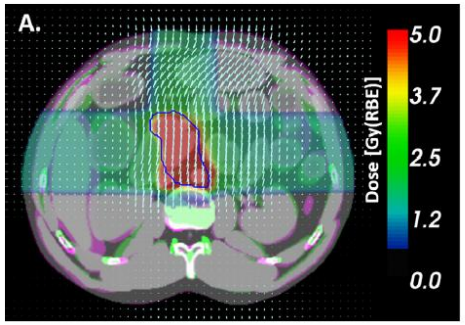
Meschini, Paganelli et al. Med Phys 2020

MRI-guidance @ CNAO: virtual 4DCT in CIRT

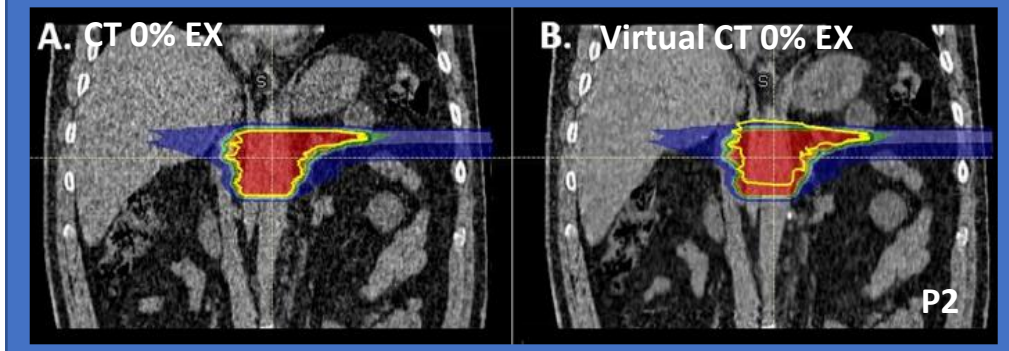
Field of view extension via the Propagation method – evaluation of clinical dosimetric plans at CNAO

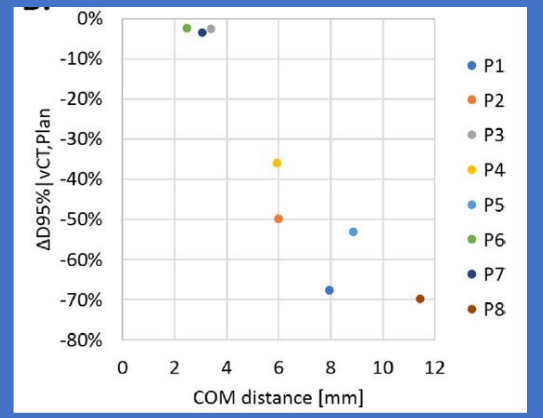


Validation on a computational phantom

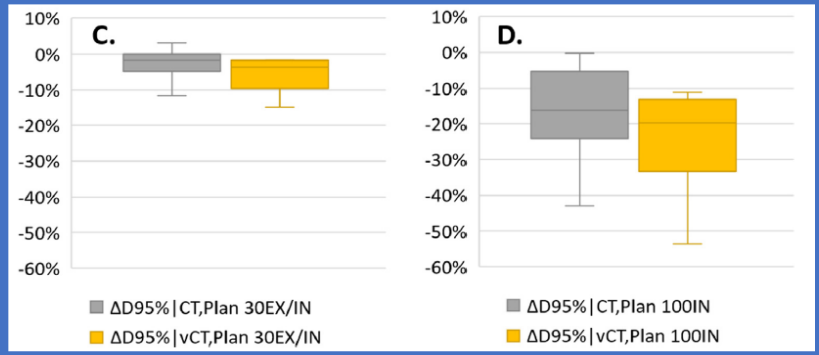


Inter-fraction





Intra-fraction



V validated and tested on clinical plans

V effectiveness of the gating procedure (intra)

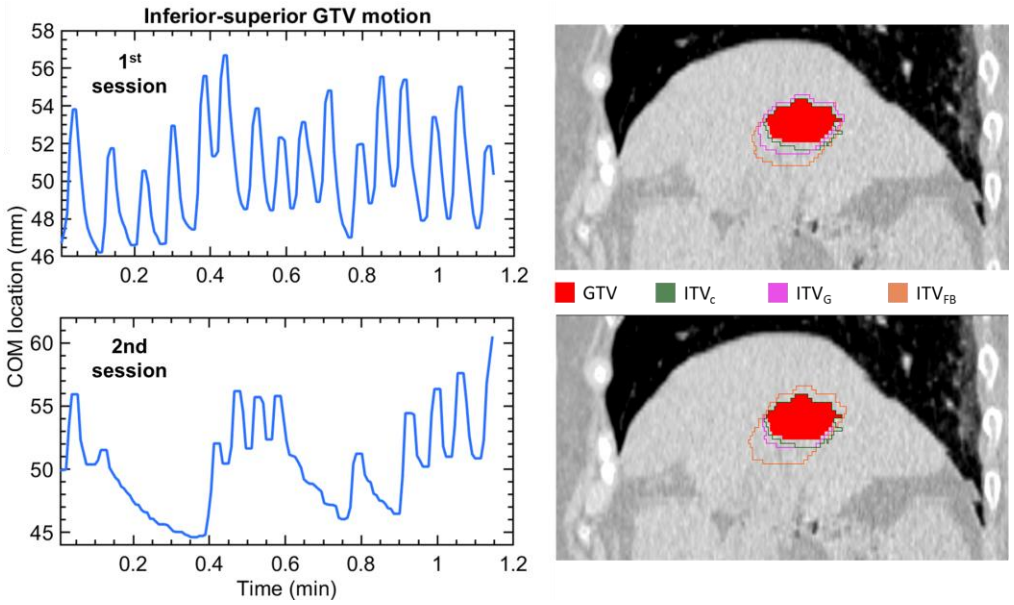
X variations wrt the plan (inter): need for in-room imaging (!!)

~ OK propagation but better a full FOV acquisition

Meschini, Vai, Paganelli et al. Z Med Phys 2020

MRI-guidance @ CNAO: gating robustness in CIRT

- Fast 2D cine-MRI used for respiratory motion
- Propagation of the tumor contour on cineMRI frames (1.13m acquisition)



- Quantification and Internal Target Volume (ITV) definition
  - Clinical approach **ITV_C**: consider gating motion as seen in the 4DCT
  - Cine-MRI gated approach **ITV_G**: consider gating motion as seen in cine-MRI
  - Cine-MRI free breathing approach **ITV_{FB}**: consider full motion as seen in cine-MRI

Added margins [mm]: median (iqr)

ITV_C	ITV_G	ITV_{FB}
3.40 (1.57)	2.18 (2.23)	9.71 (6.99)*

* Significant differences (5%)

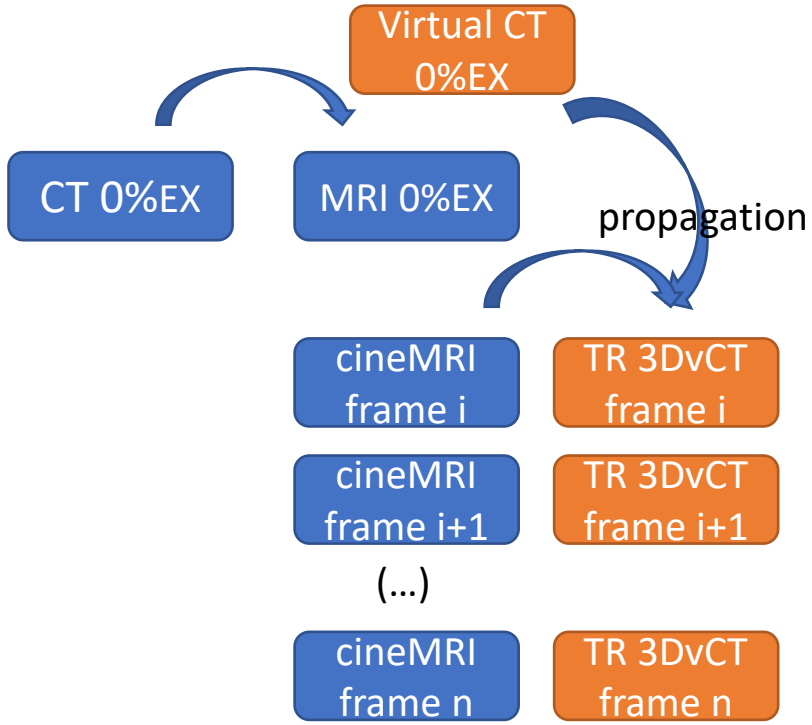
V effectiveness of the gating procedure implemented at CNAO

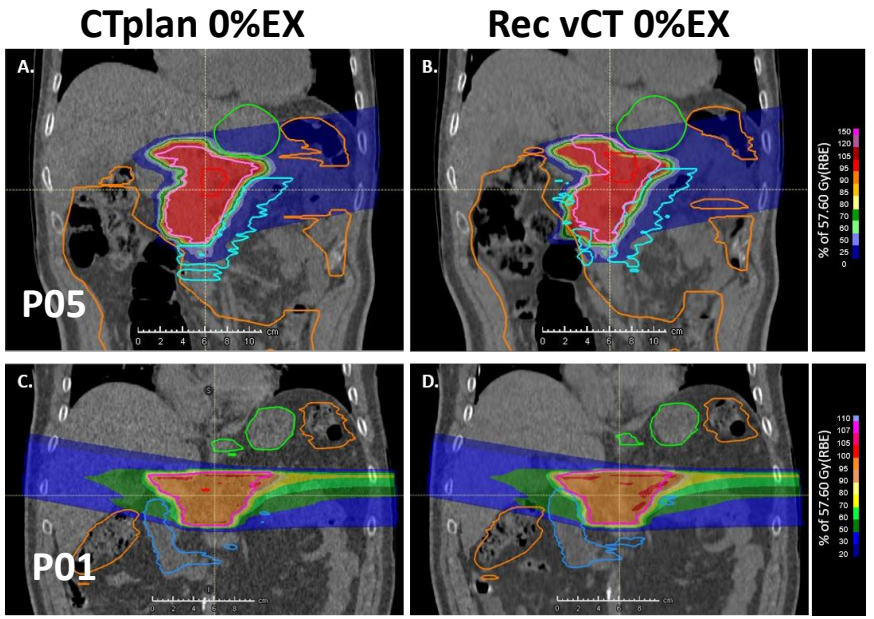
X 2D analysis

Kalantzopoulos, Meschini, Paganelli et al. Phys Med 2020

MRI-guidance @ CNAO: time-resolved 3DCT for offline treatment robustness evaluation in CIRT

Combination of virtual CT and Propagation to derive time-resolved 3DvCT





CNAO
Centro Nazionale di Adroterapia Oncologica

P05: high inter and intra-fraction motion - ΔD95 up to 16%

P01: limited inter and intra-fraction motion - ΔD95 < 5%

V effectiveness of the gating procedure (intra)
X variations wrt the plan (inter): need for in-room imaging (!!)
X still not true time-resolved 3D

The method can be adopted to test RBE-weighted 4D particle dose calculation for non-periodic motion [*Steinsberger&Graeff Phys Med 2021*]

…WORK IN PROGRESS…

Similar approach applied for protons by Rabe et al. – POSTER @4D Treatment Workshop

Conclusions/open discussion: how can we better see what we treat?

- 4DCT is the standard but needs to be improved (e.g. motion artifacts) and complemented with motion modelling techniques or alternative imaging techniques for robust plan optimization
- In-room imaging is required to account for inter-fraction variations (differences from planning to in-room condition), but needs to be improved in terms of image quality and volumetric assessment *[Landry et al. Med Phys, 2018, Mori et al. Med Phys 2018]*
- For intra-fraction motion detection, should we still rely just on external surrogates? these may be supported/complemented by motion modelling techniques
- Image-based motion models and dose variations models can be use to support robust treatment planning and offline in-room dose verification – for tracking they should be implemented online
- Motion models and dose variations models present limitations (as discussed above, e.g. DIR accuracy) – validation needed *[Brock et al.; Paganelli et al. Med Phys 2018]*; overcome by artificial intelligence ? *[Mylonas et al. JMIRO 2021]*
- MRI-guidance could play a relevant role thanks to 4DMRI and time-resolved imaging
- Still far to be implemented clinically in PT – preliminary studies for MRI-guided proton therapy, no for carbon ions *[Hoffmann et al. Rad Oncol, 2020]*
- MRI can be anyhow used to support the clinical workflow for robust treatment planning and offline dose verification

Acknowledgments

CartCasLab

Prof. Guido Baroni
Gabriele Belotti, MSc
Noemi Garau, MSc
Letizia Morelli, MSc
Marco Zampini, MSc
Anestis Nakas, MSc

CNAO
Centro Nazionale di Adroterapia Oncologica

Alessandro Vai
Silvia Molinelli
Mario Ciocca

Andrea Pella
Giulia Fontana
Rosalinda Ricotti

Luca Anemoni
Sara Imparato
Viviana Vitolo
Amelia Barcellini
Ester Orlandi

OTHERS…

Giorgia Meschini, PhD
Giulia Buizza, PhD
Prof. Marco Riboldi
Moritz Rabe, MSc
Christopher Kurz, PhD
Prof. Guillaume Landry
Chiara Gianoli, PhD
Fattori Giovanni, PhD
Riccardo Via, PhD
Prof. Paul Keall

Thanks for listening!

POLITECNICO MILANO 1863

CartCasLab

Chiara Paganelli, PhD
chiara.paganelli@polimi.it