Heavy Ion Therapy Research Integration

Imaging in particle therapy

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

IN SUPREMÆ DIGNITATIS · 1343 ·

"This material was prepared and presented within the HITRIplus **Specialised Course on Heavy Ion Therapy Research,** and it is intended for personal educational purposes to help students; people interested in using any of the material for any other purposes (such as other lectures, courses etc.) are requested to please contact the authors

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Outline

- Image guided particle therapy
- Imaging methods taking advantage of nuclear interactions
- Proton Computed Tomography
- Conclusions

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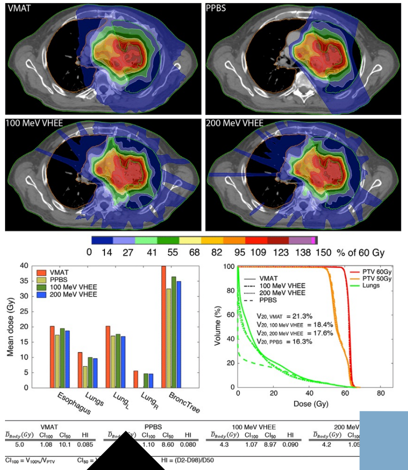
Particle therapy workflow

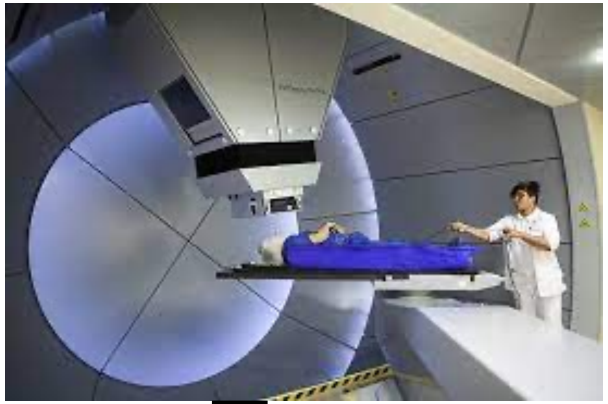
Consultation

Treatment planning

Treatment delivery (few weeks)

Follow-up





CT scan
Structures
Dose prescription

Usually after N weeks:
CT scan with structures

Imaging in particle therapy

Pre-treatment:

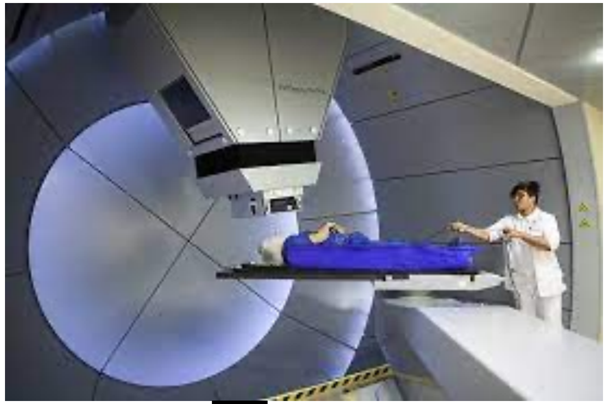
Anatomical&functional patient representation

Delineation

Input for dose calculation (Treatment Planning)

- Computed Tomography
  - Single Energy CT
  - Dual Energy CT
- Magnetic Resonance Imaging (MRI)
- Single Photon Emission CT (SPECT)
- PET Positron Emission Tomography (PET)

Treatment delivery (few weeks)



Usually after N weeks:
CT scan with structures

Follow-up

Imaging in particle therapy

“Image-guided radiotherapy (IGRT) is the process of frequent imaging (i.e. 2D or 3D) the patient in the treatment room during a course of radiotherapy to guide the treatment process" [Verellen et al., Nat Rev Cancer, 7(12):949{960, dec 2007

Pre-treatment:

Anatomical&functional patient representation

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  - Dual Energy CT
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- PET Positron Emission Tomography (PET)

Treatment:

patient daily set up, trigger for adaptation, Input for dose calculation and range monitoring

- In-room image guidance
  - X-ray
  - Cone –beam CT
  - Future: MRIgPT
- During treatment
  - PET
  - prompt gamma
  - Charged fragments
- proton CT (pCT) or proton radiography

Follow-up

s

Imaging in particle therapy

See also J. Seco, M.F. Spadea, Imaging in particle therapy: State of the art and future perspective, Acta Oncologica 54, 9, 1254-1258, 2015

Pre-treatment:

Anatomical&functional patient representation

Delineation

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  - Charged fragments
- proton CT (pCT) or proton radiography

Post-treatment:

Tumor response

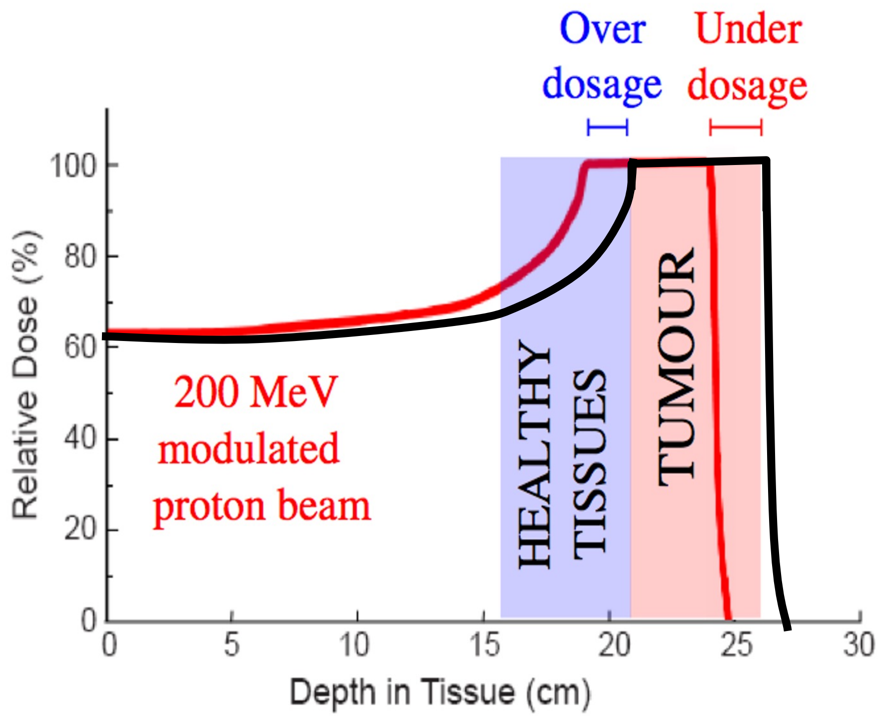
Radiation toxicity

Dose-effect modeling

patient follow-up and post-treatment assessment

- MRI
- CT

Range uncertainties



Zhu X, Fakhri GE. *Theranostics. 2013;3(10):731-740.*

safety margins → 2.5-3% + 1-3 mm

Imaging in particle therapy: uncertainties

Patient related

- daily positioning on the couch
- internal organ motion
- changes in air cavities
- tumour regression
- weight loss

Physics related

- CT HU (e.g.calibration apparatus)
- conversion to proton stopping power
- dose calculation uncertainties

Other sources

- RBE values
- Tumor heterogeneity
- Contouring uncertainties
- Reconstruction artifacts in CT
- Machine related

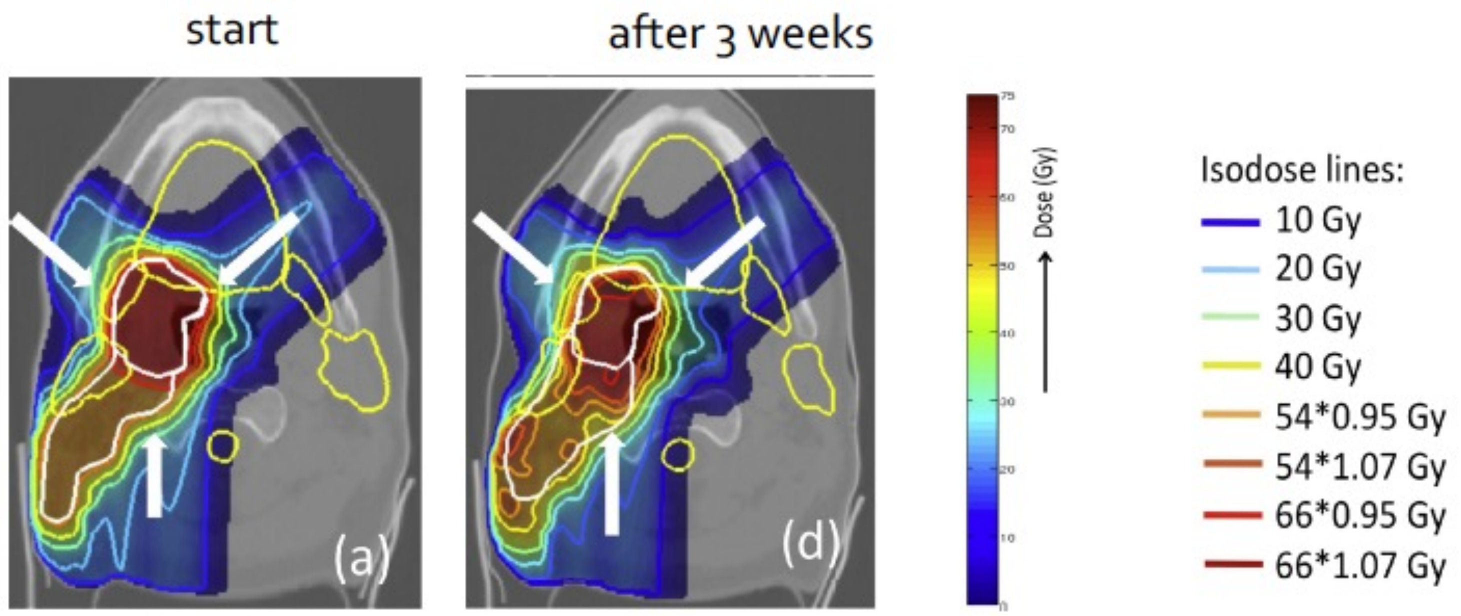
Courtesy of A. Del Guerra. Krakow 2015

Dose impact of uncertainties

- Very precise…

- But different uncertainties can lead to dose distortions…

From Kraan et al Int J Radiat Oncol Biol Phys 2013;87(5):888-96.



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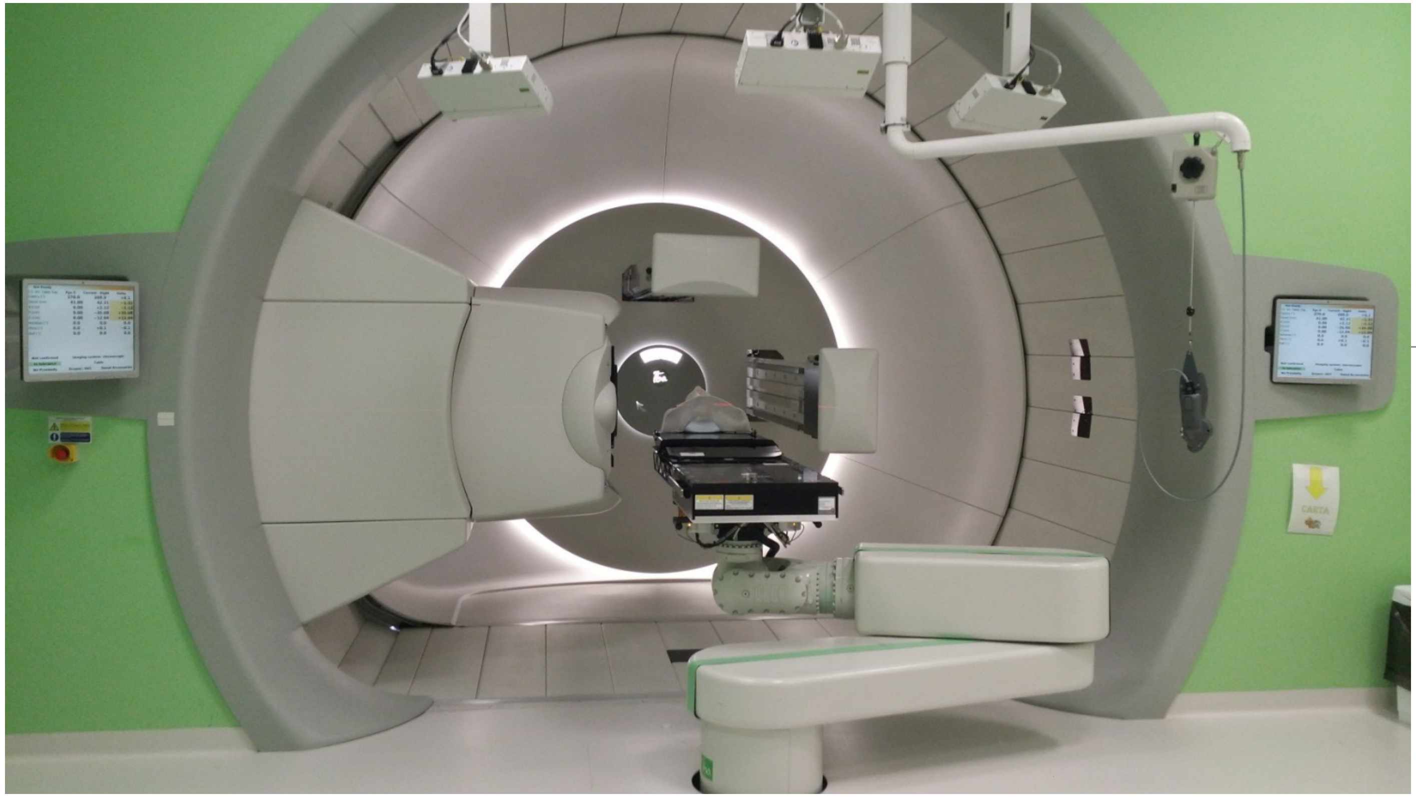
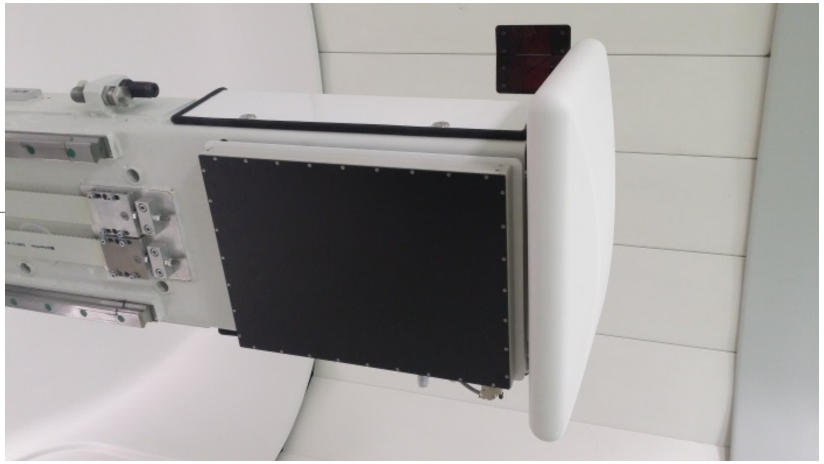




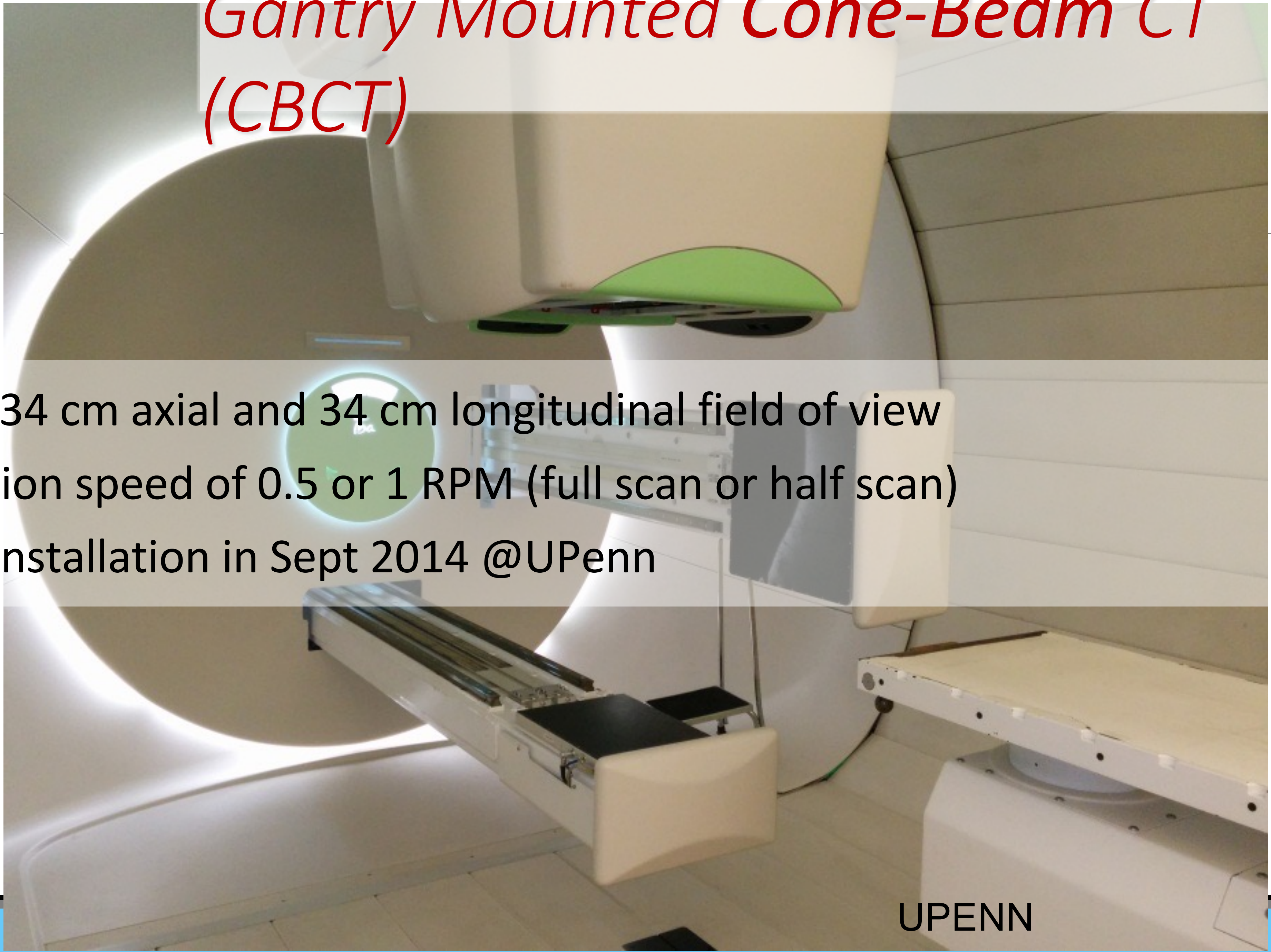
standard in PT: two orthogonal KV images
Daily alignment and correction with no action level
It allows very accurate bone-based positioning
Fully adequate for many classical indications of PT
Requires larger “margins” if inter/intrafraction motion is an issue

Gantry Mounted ***Cone-Beam*** *CT (CBCT)*

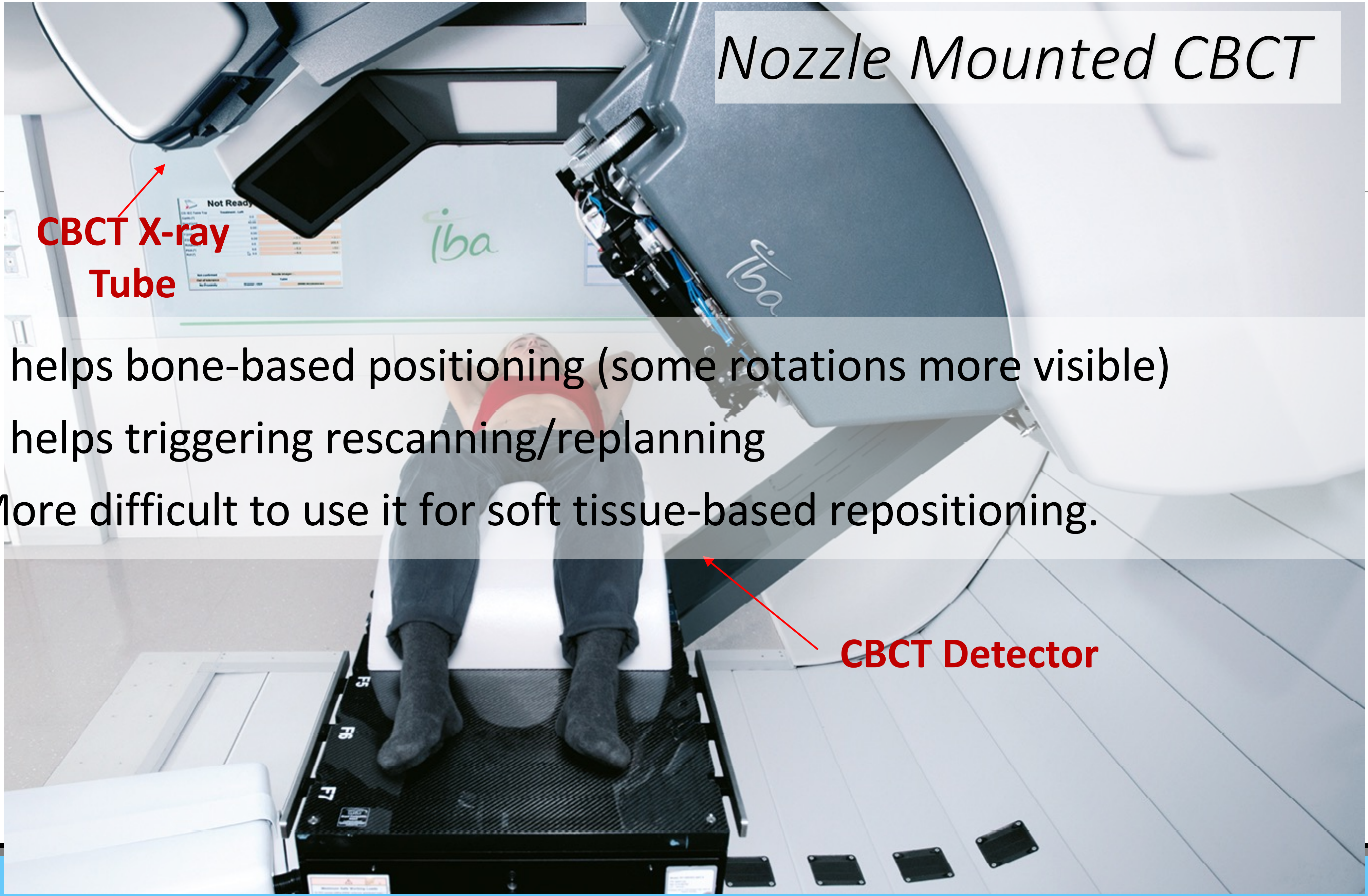
FOV: 34 cm axial and 34 cm longitudinal field of view

Rotation speed of 0.5 or 1 RPM (full scan or half scan)

First installation in Sept 2014 @UPenn



Nozzle Mounted CBCT

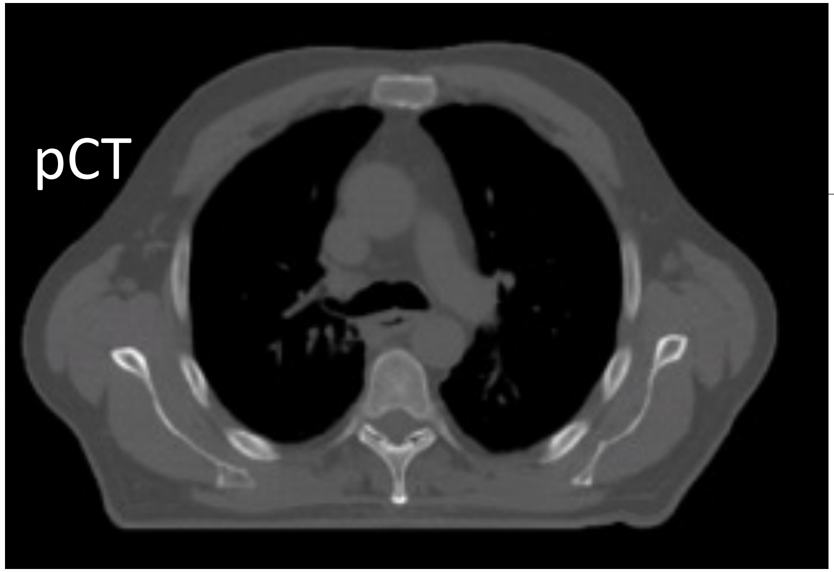


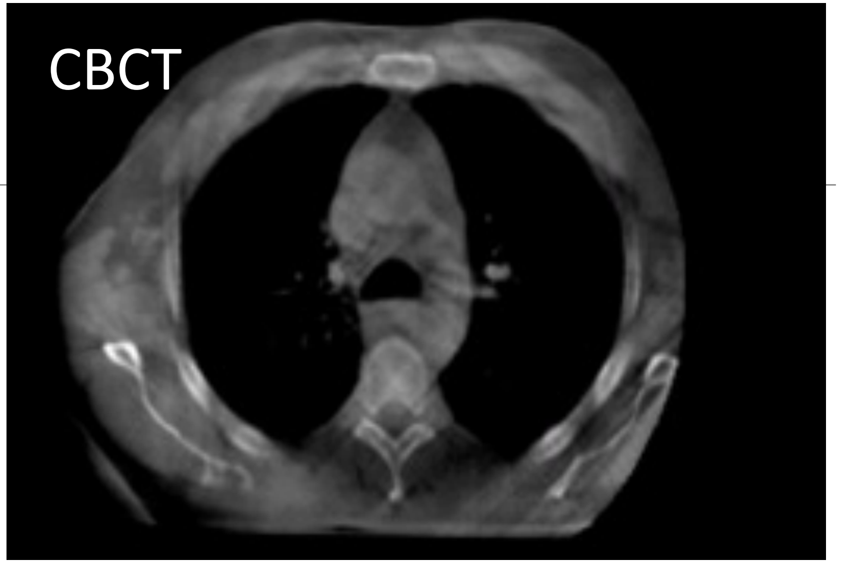
It helps bone-based positioning (some rotations more visible)

It helps triggering rescanning/replanning

More difficult to use it for soft tissue-based repositioning.

CBCT by itself may not be sufficient





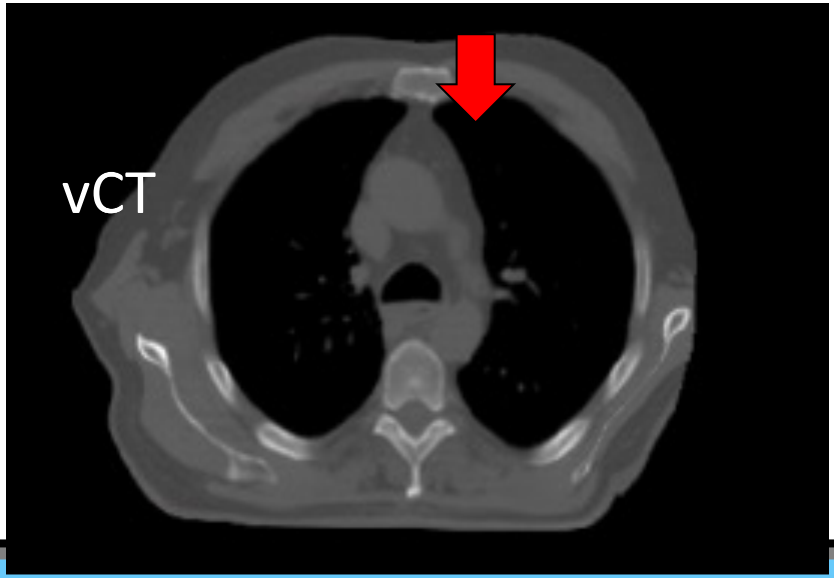
Method works in most cases

Limitations:

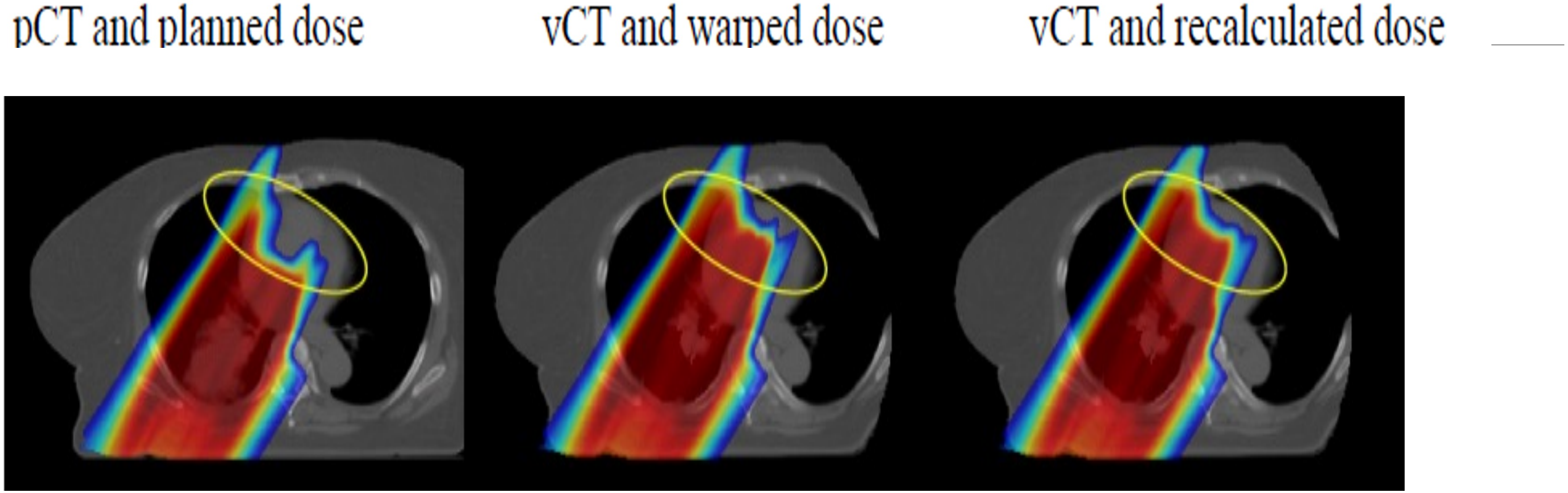
(1) Complex anatomical change not handled correctly by deformable image registration (DIR) software

(2) Subtle changes in lung/tumor density not accounted for

C Veiga et al, IJROBP 95 549 (2016)

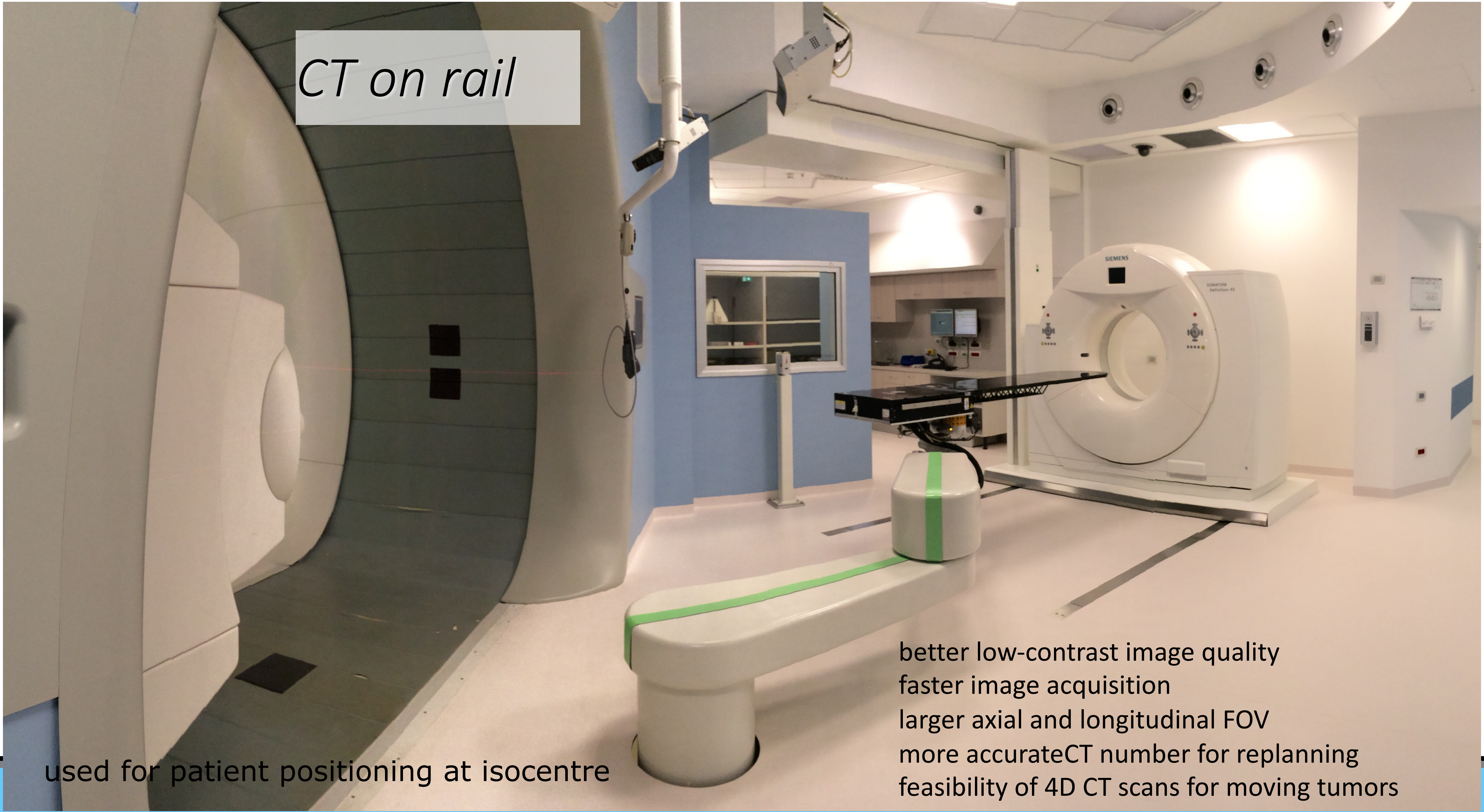


From CBCT to "dose of the day"



IJROBP Veiga et al 2016

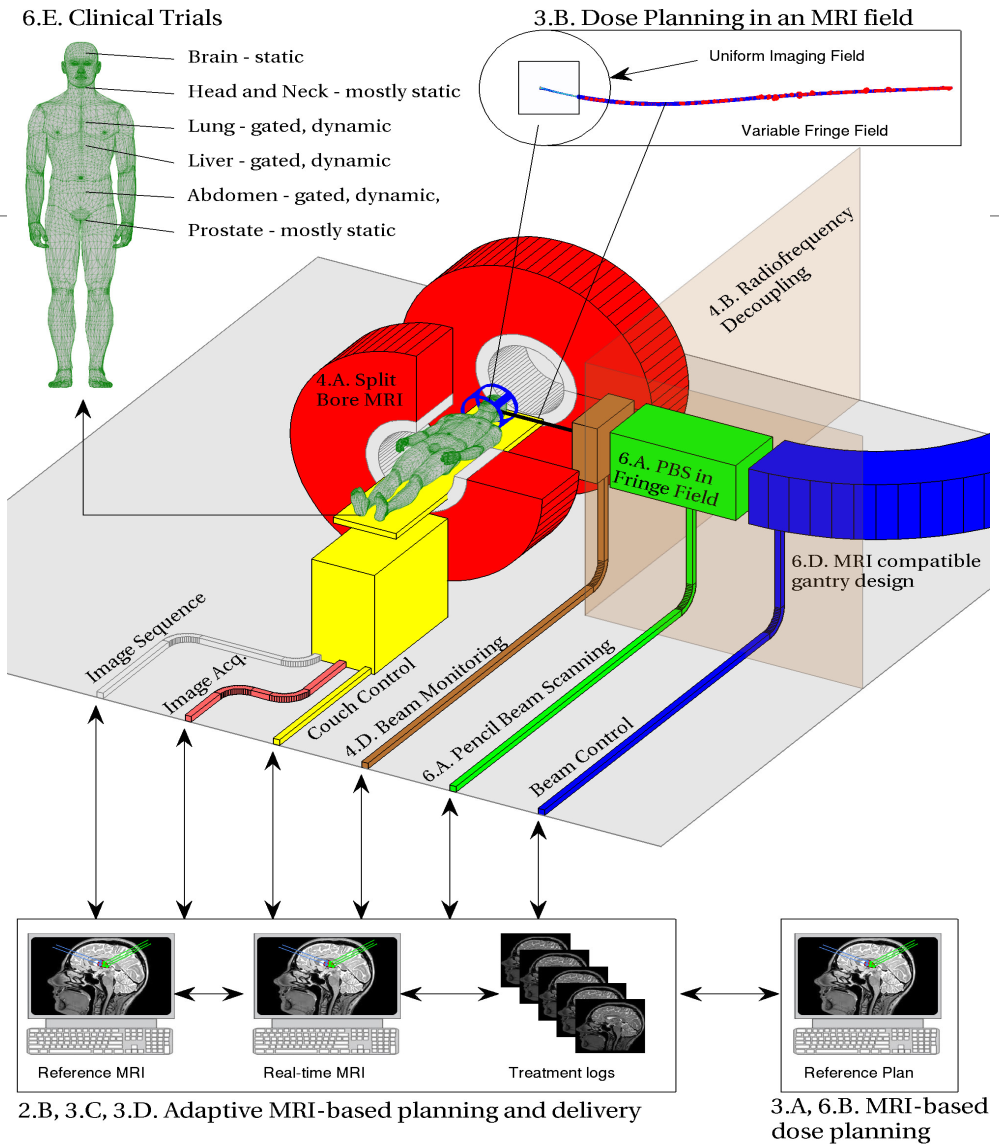
CT on rail



used for patient positioning at isocentre

better low-contrast image quality
faster image acquisition
larger axial and longitudinal FOV
more accurateCT number for replanning
feasibility of 4D CT scans for moving tumors

The competition: MR guided Particle Therapy (MRgPT)



Oborn BM, Dowdell S, Metcalfe PE, Crozier S, Mohan R, Keall PJ. Future of medical physics: Real-time MRI-guided proton therapy. Med Phys. 2017 Aug;44(8):e77-e90. doi: 10.1002/mp.12371. Epub 2017 Jul 4. PMID: 28547820.

Detailed anatomical information
Better for soft tissues
No ionising radiation used

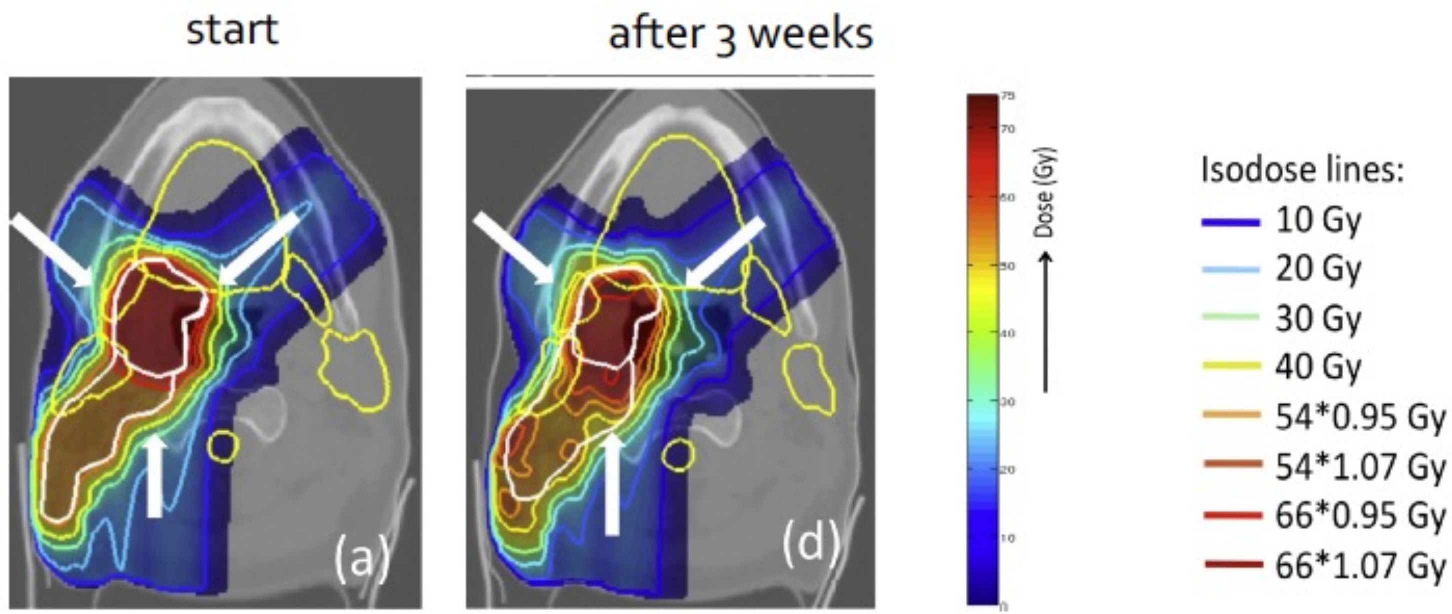
Electromagnetic interactions between the MRI and PT systems
integration of MRgPT workflows in clinical facilities
proton dose calculation algorithms in magnetic fields

Dose impact of uncertainties

- Very precise…

- But different uncertainties can lead to dose distortions…

From Kraan et al Int J Radiat Oncol Biol Phys 2013;87(5):888-96.



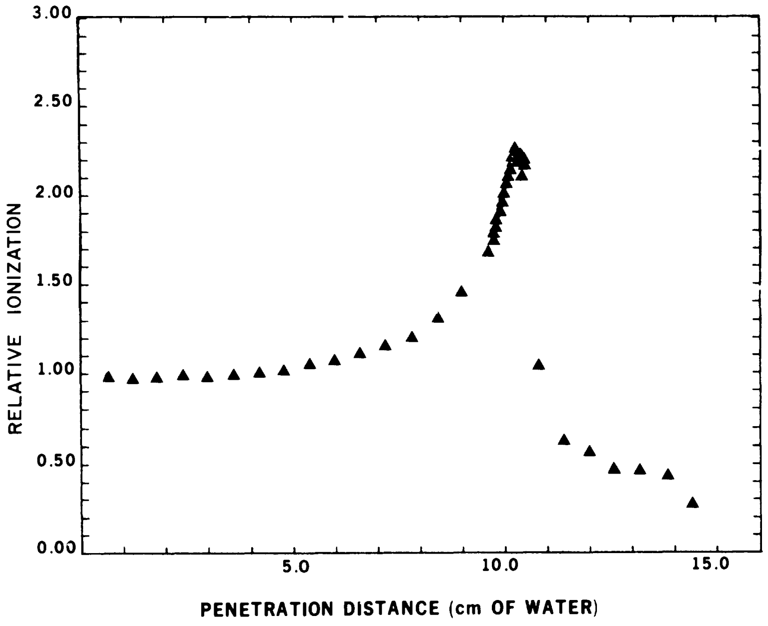
In vivo range verification offers the possibility to check the accuracy of the beam delivery

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

Nuclear interactions in particle therapy

"Physical Measurements with High-Energy Radioactive Beams"

A. Chatterjee, W. Saunders, E. L. Alpen, J. Alonso, J. Scherer and J. Llacer Radiation Research, Vol. 92, No. 2 (Nov 1982), pp. 230-244



BEVALAC, LBL, USA, 19Ne beams obained by nuclear fragmentation of 20Ne beams on Be target

Abstract

"Physical measurements were made with ***high-energy radioactive beams (positron emitters) produced as secondary particles from a heavy-particle accelerator***. Data are presented for water-equivalent thickness of a silicon diode,a comparison of Bragg peak ionization depth vs stopping depth,and differential stopping depths when a beam is intercepted by heterogeneous materials in the orthogonal direction. A special positron-emitting beam analyzing (PEBA) system was used to form images of the stopped radioactive beam. ***These measurements will have direct impact on charged-particle radiotherapy, since the precise range of beams of charged particles to targets within patients can be measured and used for treatment planning. Also, during the treatments the stopping point of the beam can be monitored to verify that the treatment is being delivered as planned.***

HITRI plus
Heavy Ion Therapy Research Integration

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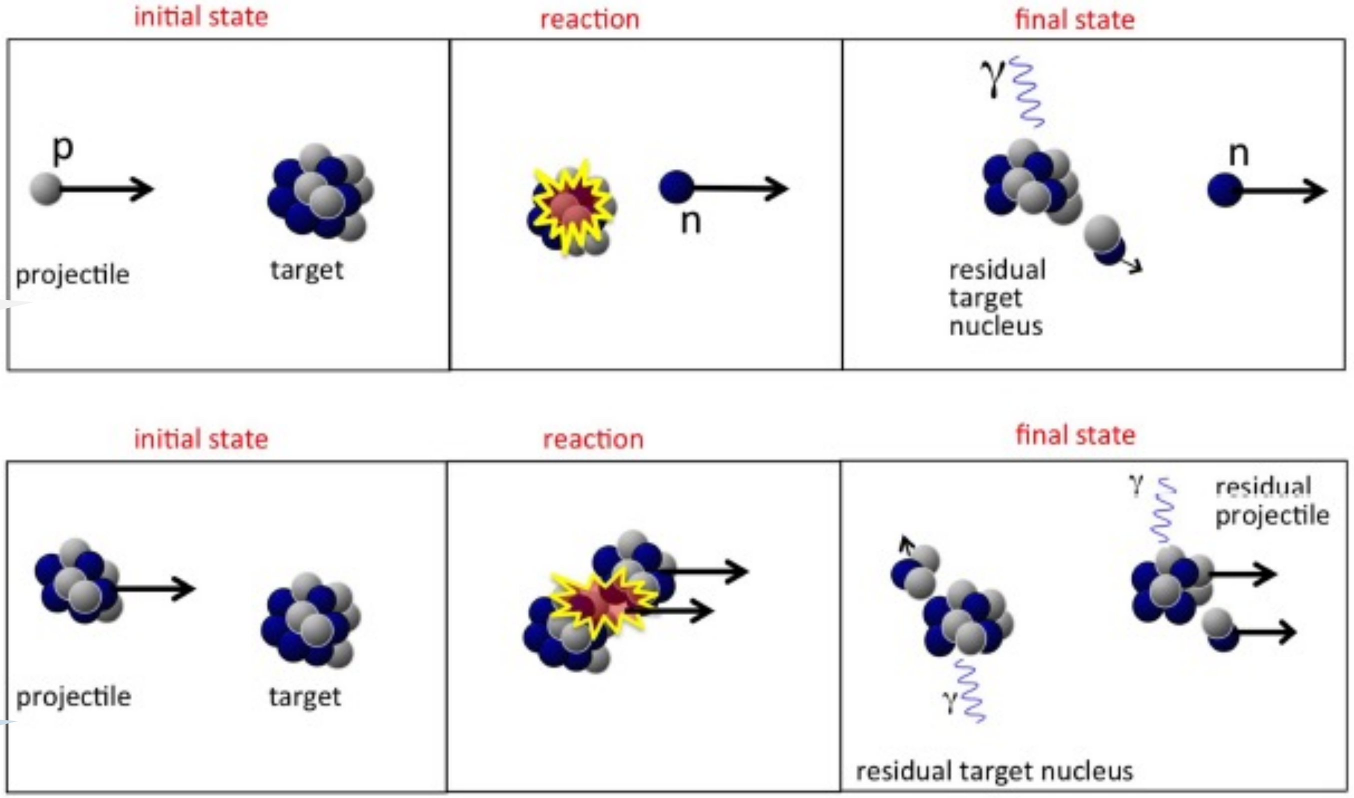
Nuclear interactions in particle therapy

Proton therapy: Example of proton nucleus interaction

Carbon therapy: Example of nucleus nucleus interaction



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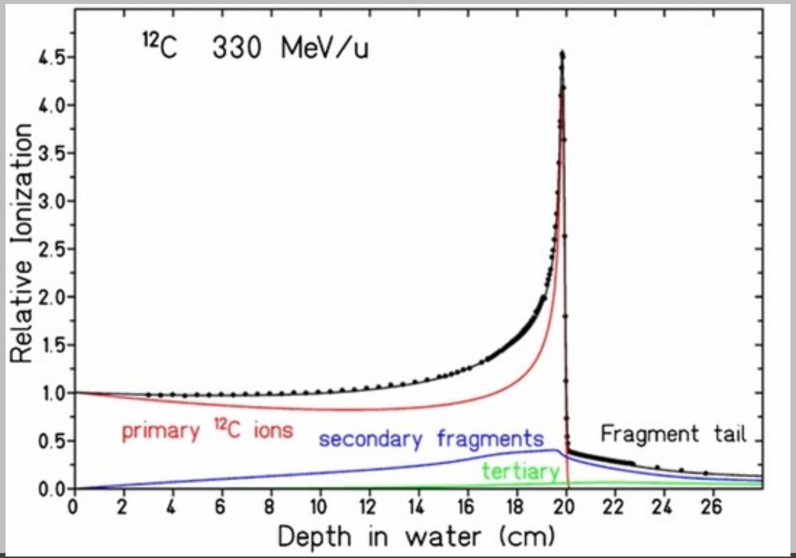
Nuclear interactions in particle therapy

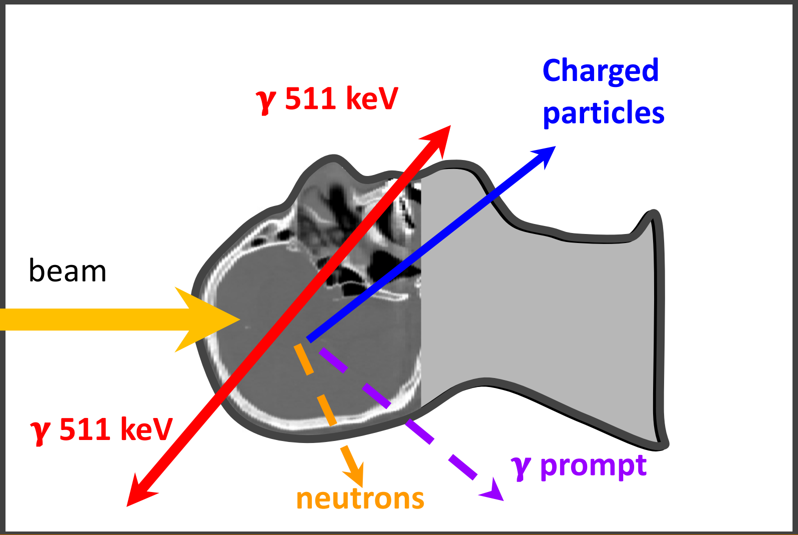


Consequences

Loss of beam fluence. For 290 MeV/u carbons: 50% of ions have nuclear reaction

The dose distributions are modified:

- Build-up region of Bragg curve
- Height of the Bragg peak.
- Carbon therapy: dose beyond the Bragg peak.
- Low energetic secondary particles --> "low dose envelope"



- Various types of secondary particles are produced. Kinematics depend on stage during nuclear reaction
  - β+ emitting isotopes → PET
  - Prompt gammas
  - Charged fragments

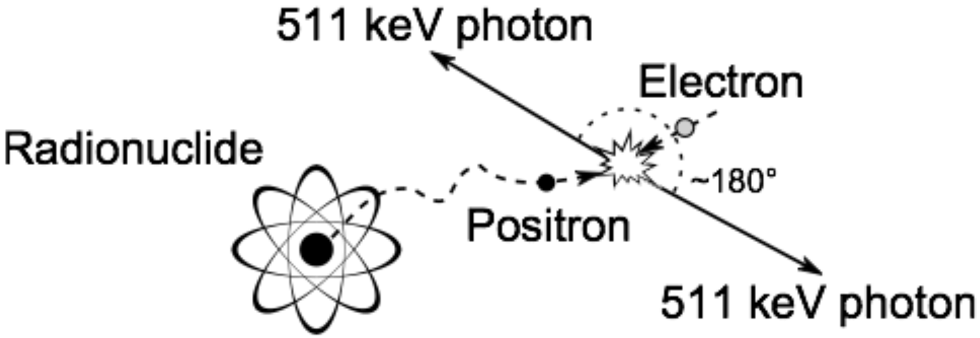
Nuclear interactions in particle therapy

- One of the ways to verify the delivered dose is by means of PET (Positron-Emission-Tomography)
- Therapeutic hadron beams produce β^+ emitters in the body

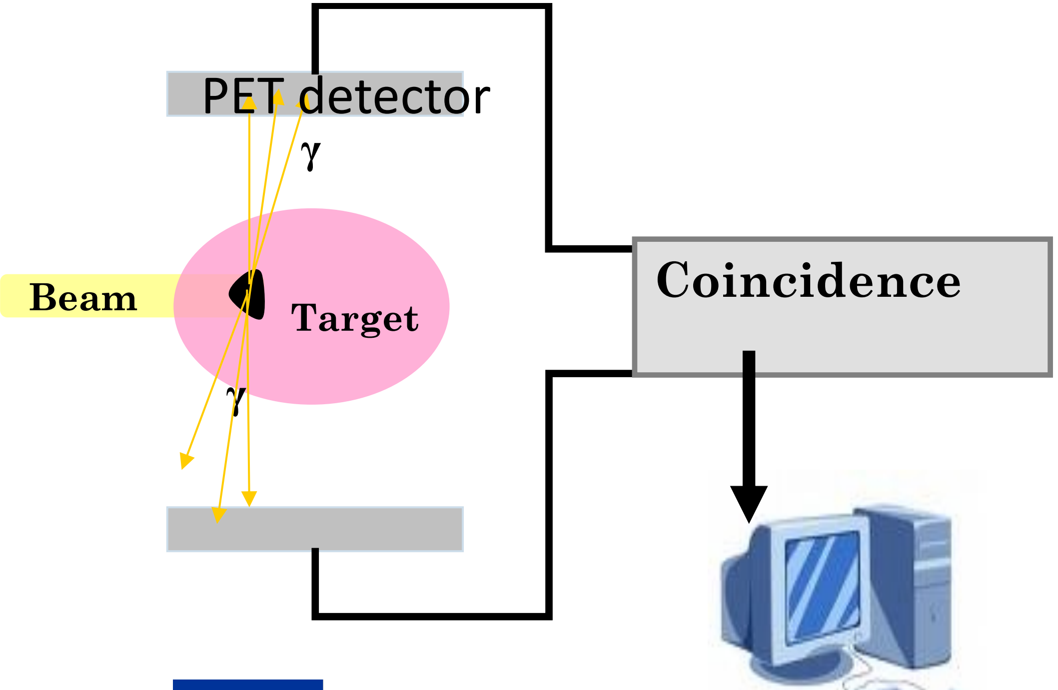
E.g. proton beam:

$p + {}^{16}O \rightarrow (p,n) + {}^{15}O \rightarrow {}^{15}N + \beta^+ + \nu \quad \tau_{15\text{-}O}=122$ s (2 min)

$p + {}^{12}C \rightarrow (p,n) + {}^{11}C \rightarrow {}^{11}B + \beta^+ + \nu \quad \tau_{11\text{-}C}=1223$ s (20 min)



PET activity=
nr of radioactive decays per time-interval

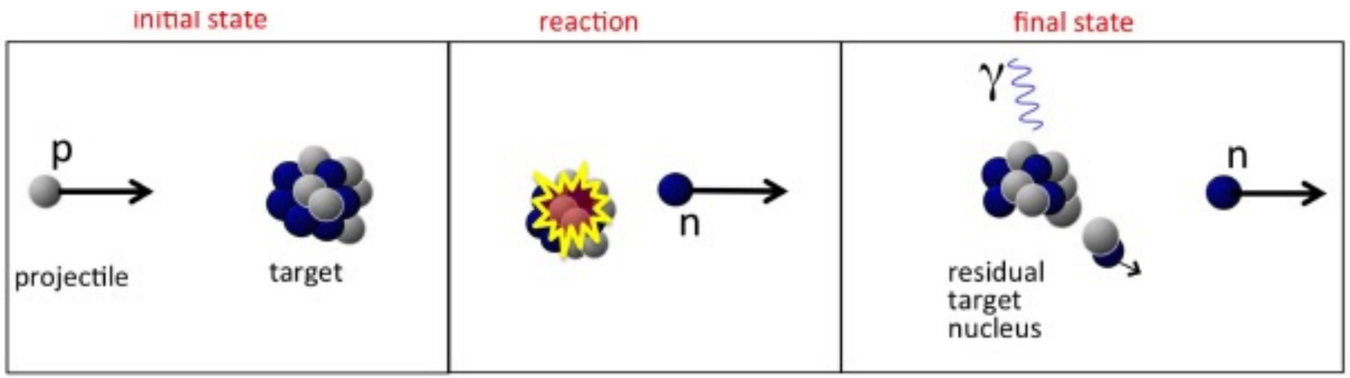


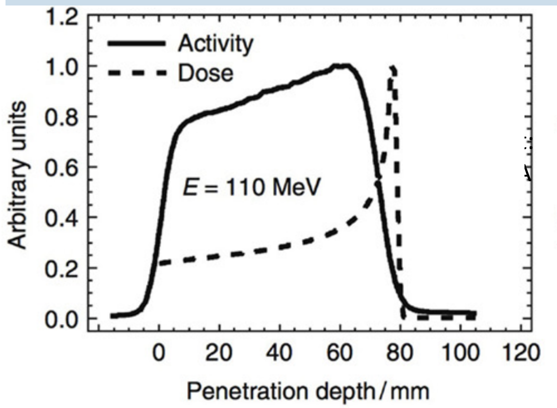
This project has received funding from t
research and innovation programme unc
2020
548

Nuclear interactions in particle therapy

Beta+ activity related with Bragg peak position!

Proton therapy: Example of proton nucleus interaction





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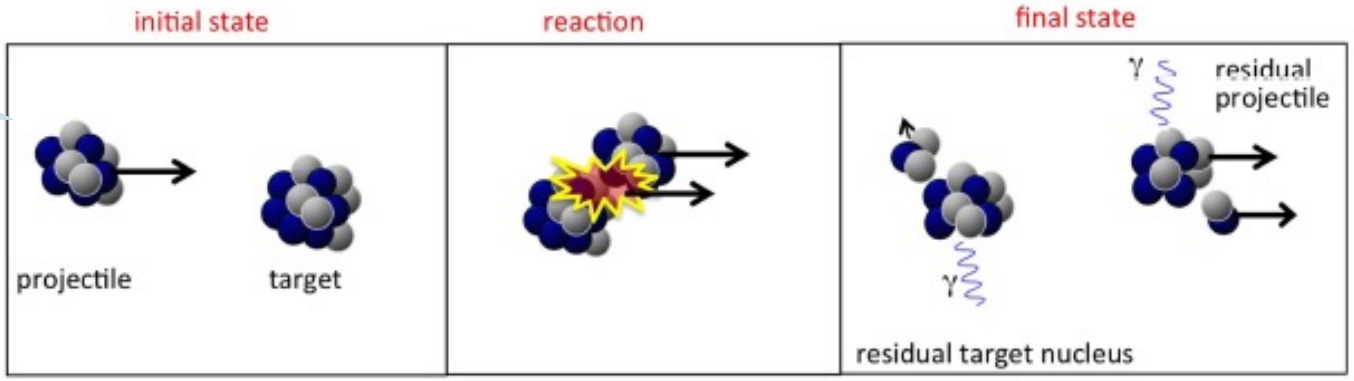
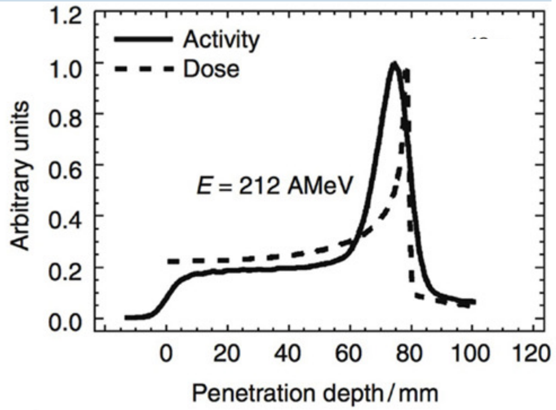




HITRIplus
Heavy Ion Therapy Research Integration

This project h... research and...

Fiedler F, et al, *Ion Beam Therapy Fundamentals, Technology, Clinical Applications*. Berlin: Springer-Verlag (2012). p. 527–43.

K. Parodi and J. Polf. “In vivo range verification in particle therapy”, Medical Physics 45, 2018

A.C. Knopf and A Lomax. “In vivo proton range verification: a review”. In:Phys Med. Biol.58.15 (2013), R131–160.

PET monitoring in particle therapy

First pioneer work by W. Enghardt et al. in the ’90 with Carbon Ions *(GSI/Bastei tomograph)*

Off-line PET = dose delivery and PET in different locations *(MGH/Heidelberg/CHIBA)*

- Advantages
  - Commercial PET scanner 360 degrees (no image artifacts)
- Disadvantages:
  - Patient re-positioning
  - Data loss of short living isotopes (e.g. ^{15}O)
  - Radio-isotope wash-out

On-line PET = dose delivery and PET in same room

➔In Room-PET: data when beam is off *(GSI/PISA-CNAO/CHIBA/MGH/HEIDELBERG)*

➔In-beam-PET: data when beam on *(PISA-Torino-CNAO/CHIBA-openPET)*

- Disadvantages:
  - Image artifacts
  - Small statistics (not much ^{11}C)

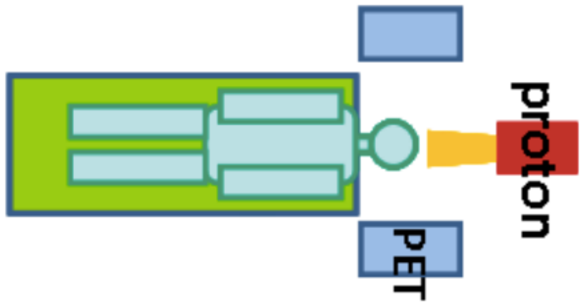
Dose delivery
+
PET

PET monitoring in particle therapy

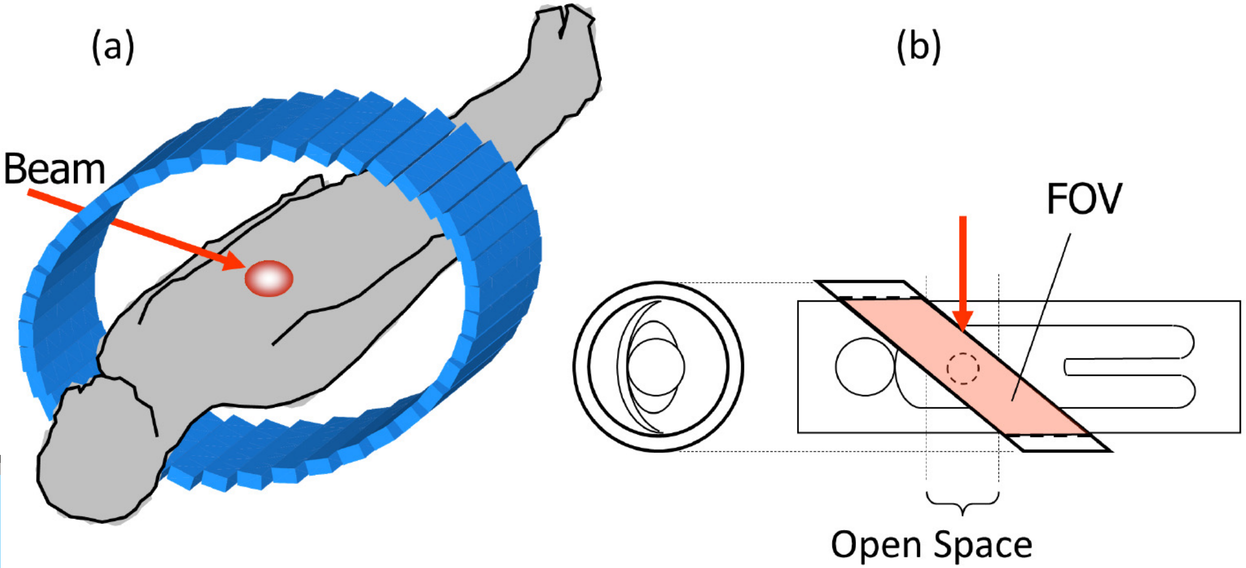
- Main problem in in-beam PET: difficult to integrate with dose delivery system, position systems, etc …

- Solutions
  - Two planes (see next)
  - Particular geometries
    - Example: Open PET system

    National Institute of Radiological Sciences, QST (NIRS), Japan



Tashima et al 2016 Phys. Med. Biol. 61 1795



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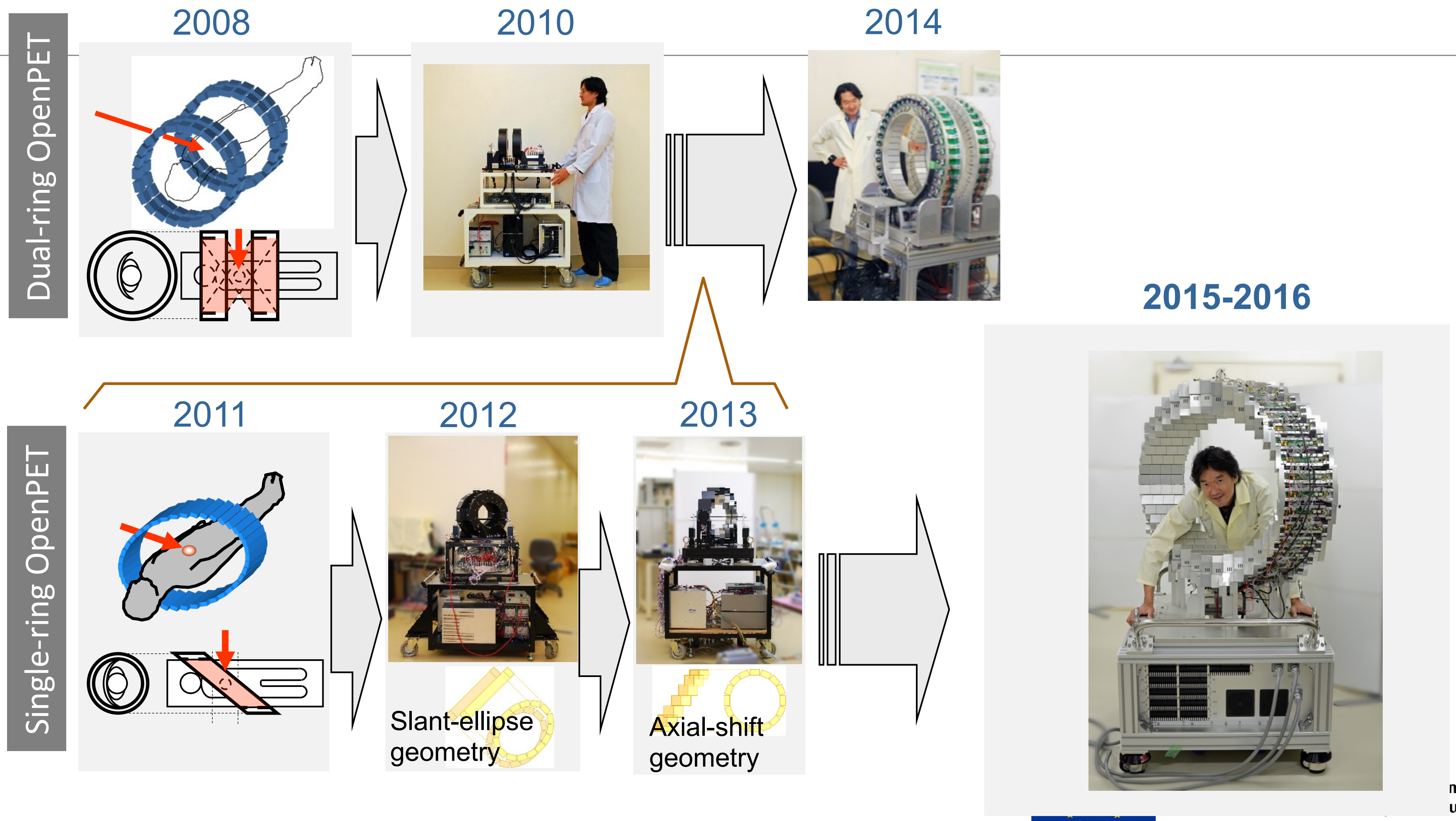
OPENPET



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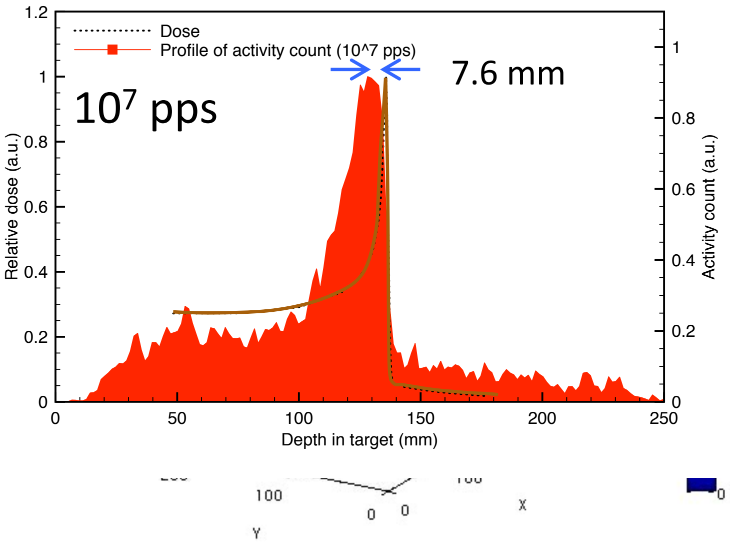
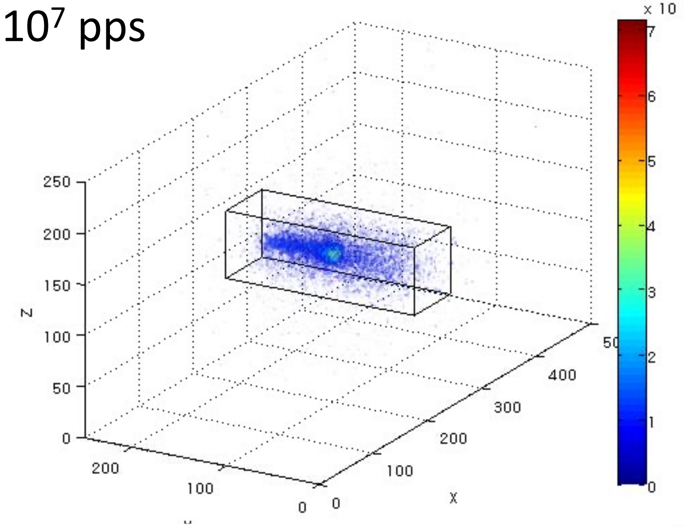
under grant agreement No 101008548

Courtesy of Taiga Yamaya

HIMAC test w ^{12}C beam

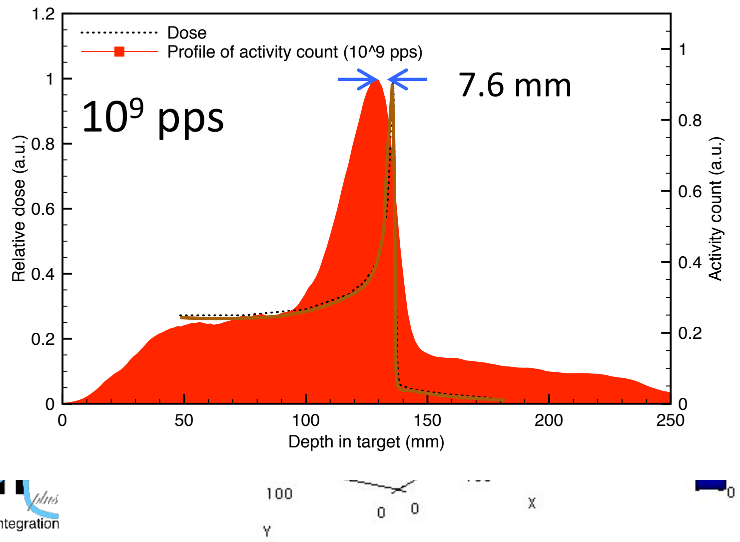
MIC2015

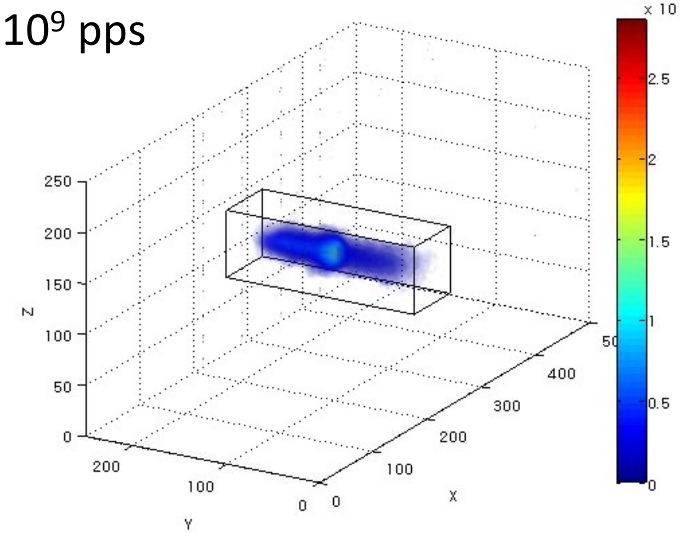




PMMA (10cm x 10cm x 30cm long)

Irradiation
C12 400 MeV/u
Time about 10s
(3 spills of 3.3s irradiation cycle).





1Gy for the case of 2x10^6 pps.

Spill off + beam off (23min)
MAP-EM
1.5 mm^3 voxel

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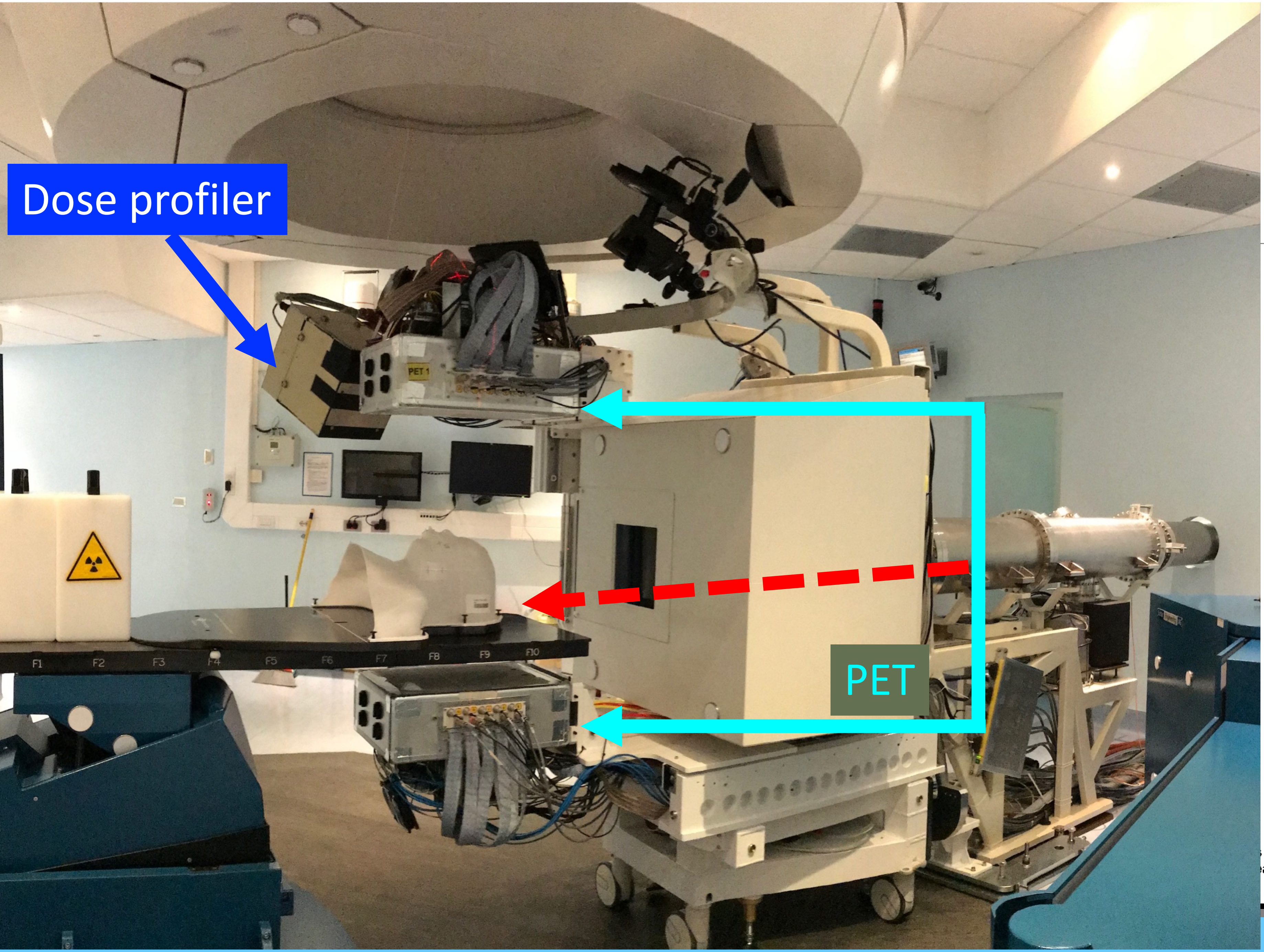
ch and innovation programme under grant agreement No 101008548

Courtesy of Taiga Yamaya



InSide

INFN

SAPIENZA
UNIVERSITÀ DI ROMA

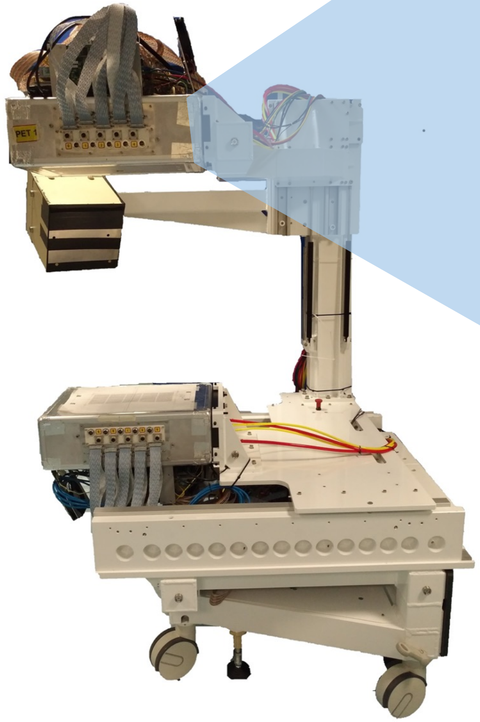
UNIVERSITÀ DEGLI STUDI DI TORINO

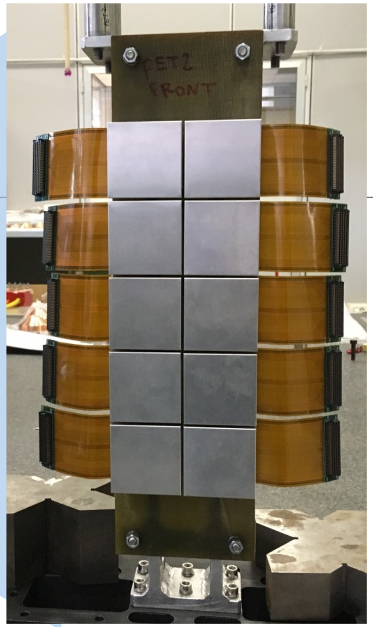
CNAO

CENTRO FERMI

PRIN 2010-2011

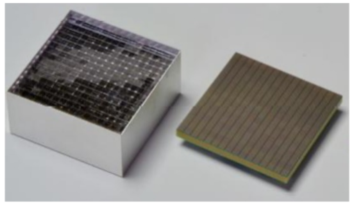
IN-BEAM PET





PET modules
256 Luthetium Fine Scintillating (LFS) pixel crystals (3 x 3 x 20mm^3) coupled to SiPMs

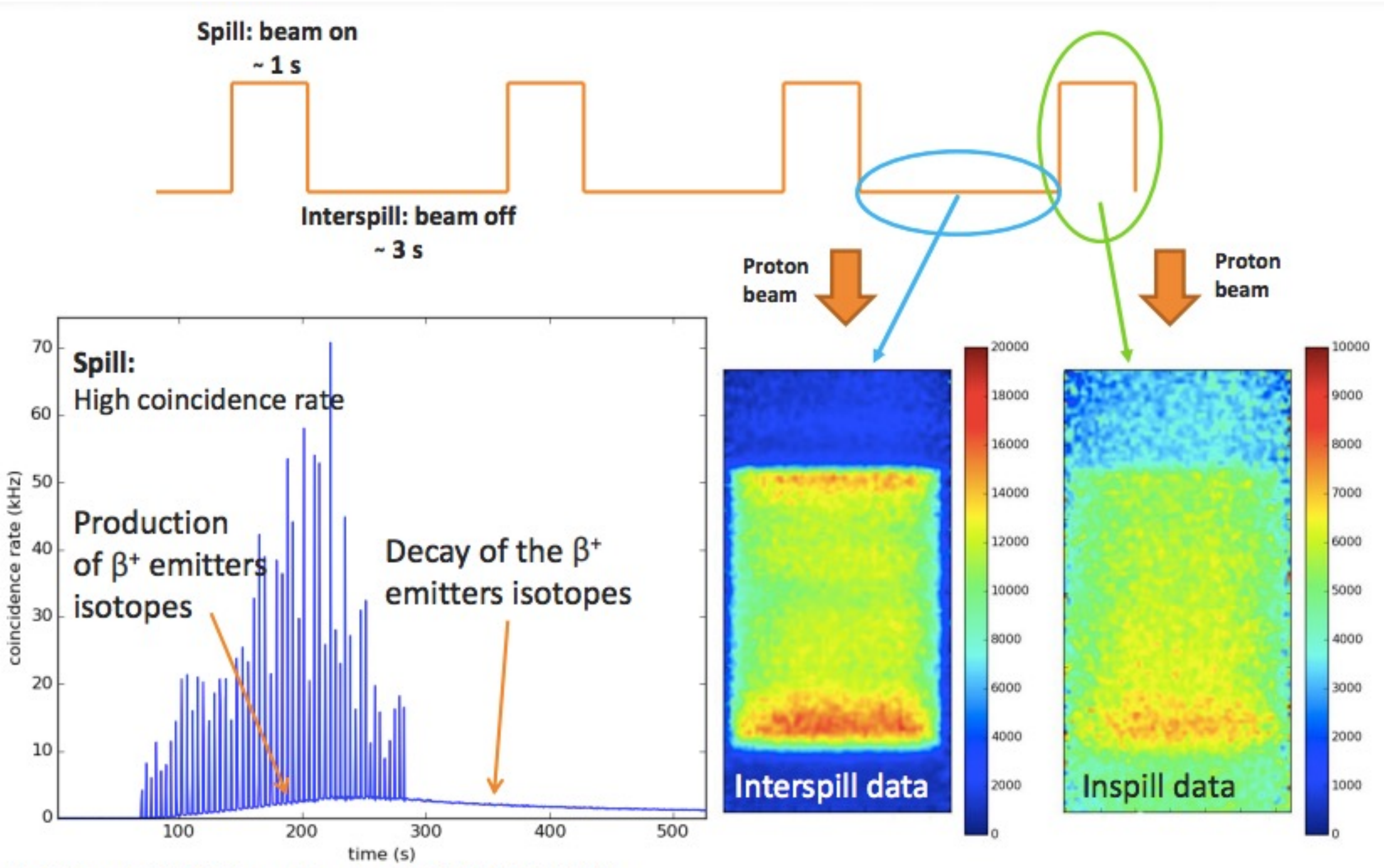
PET panel
2x5 modules
active area = 10 x 25 cm^2 @ 30 cm from the isocenter



Main features
coincidence window = 2 ns
CTR (Ge68) = 1.2 ns FWHM
Avg energy resolution = 13%
image reconstruction method: MLEM

M.G. Bisogni, et al.,
Journal of Medical Imaging 4(1), 2017

INSIDE: in-beam PET

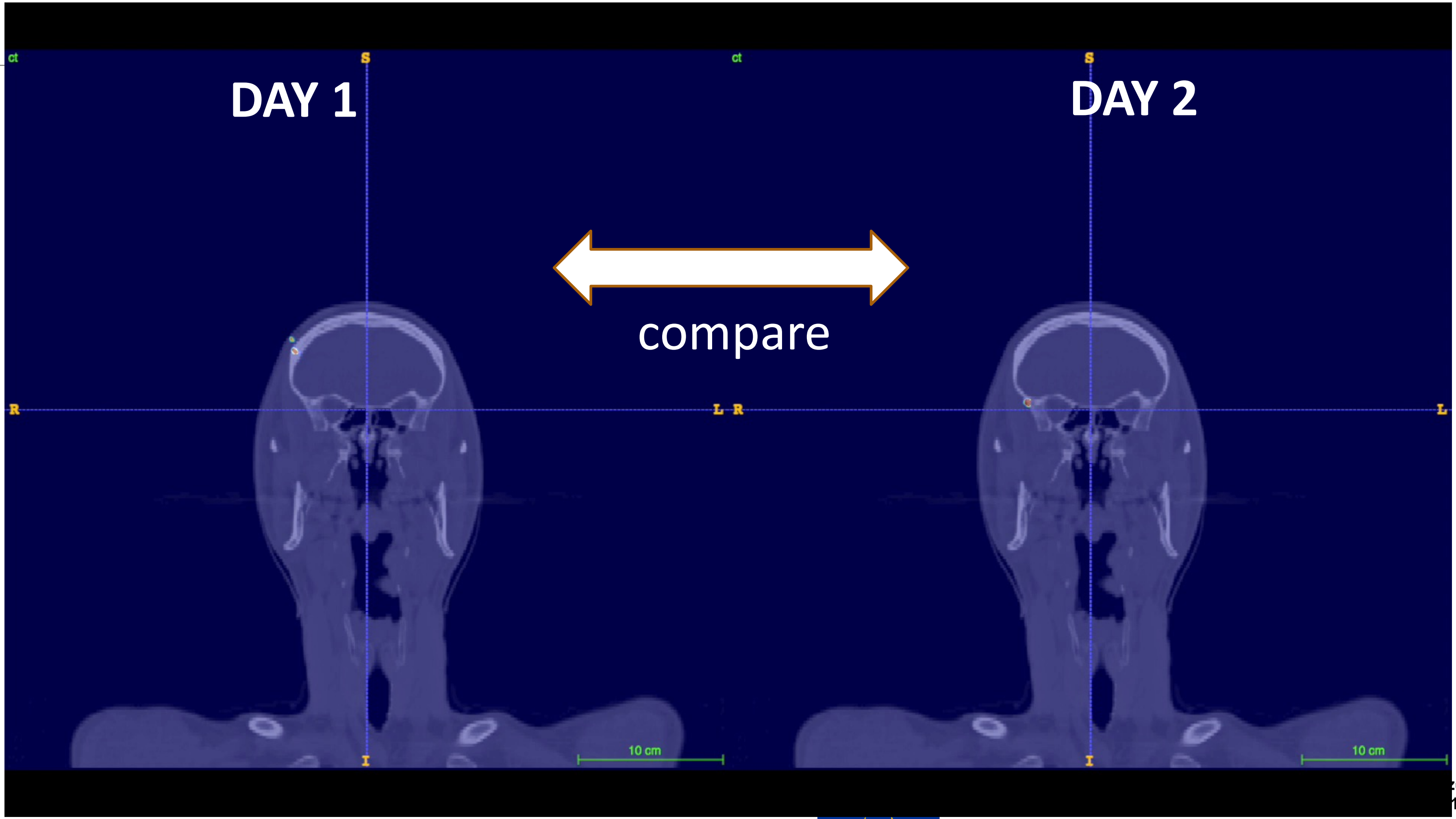


M. G. Bisogni, ENLIGHT Annual Meeting, 13/05/2017, AUH Skejby

ding from the European Union's Horizon 2020
ramme under grant agreement No 101008548

Carcinoma of the lacrimal gland
3.7 10^{10} protons
[66.3, 144.4] MeV/u (28-29)/30 fractions, 2.2 GyE
Vertex field
240 s treatment + 30 s after-treatment of data acquisition

INSIDE: in-beam PET

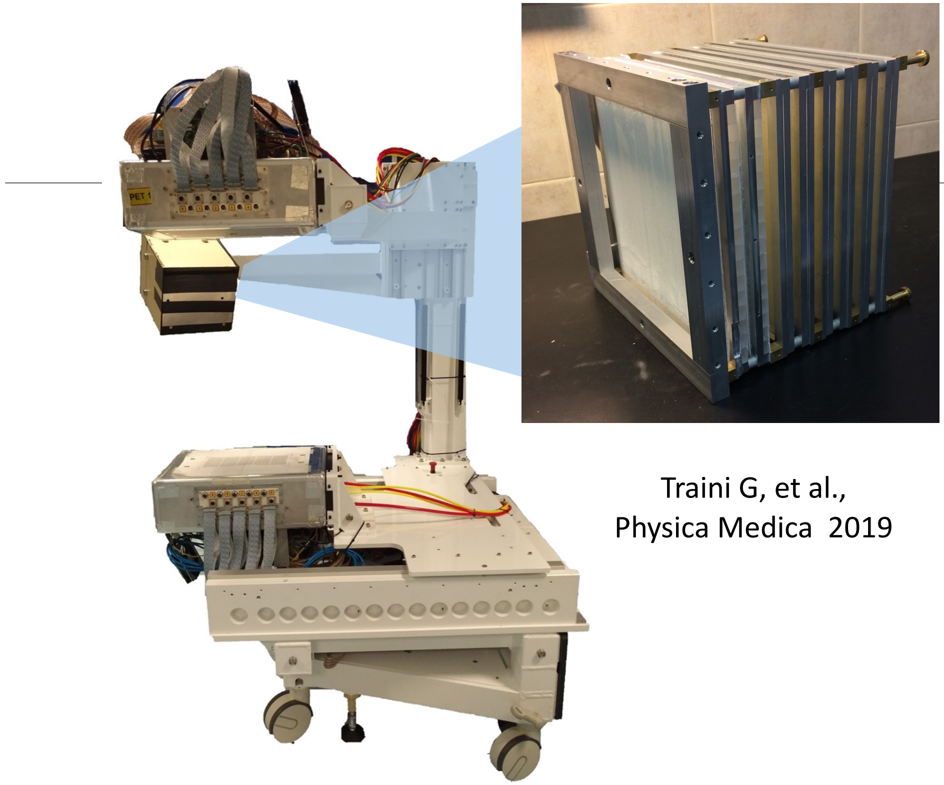


V. Ferrero et al., "Online proton therapy monitoring: clinical test of a Silicon-photodetector-based in-beam PET"
Scientific Reports, *(2018) 8:4100*

E. Fiorina et al, Front. Phys. 2021

F. Pennazio et al. :Phys.Med. Biol.63 2018

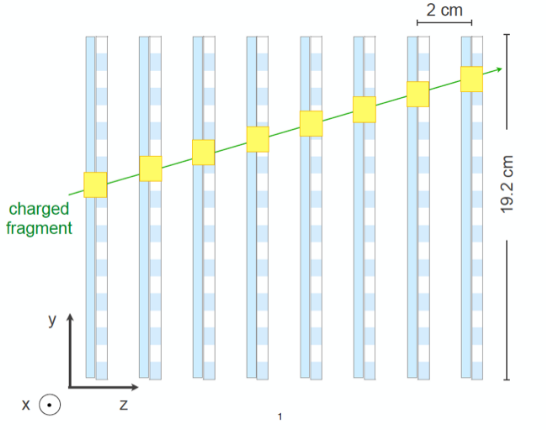
DOSE PROFILER



Traini G, et al.,
Physica Medica 2019

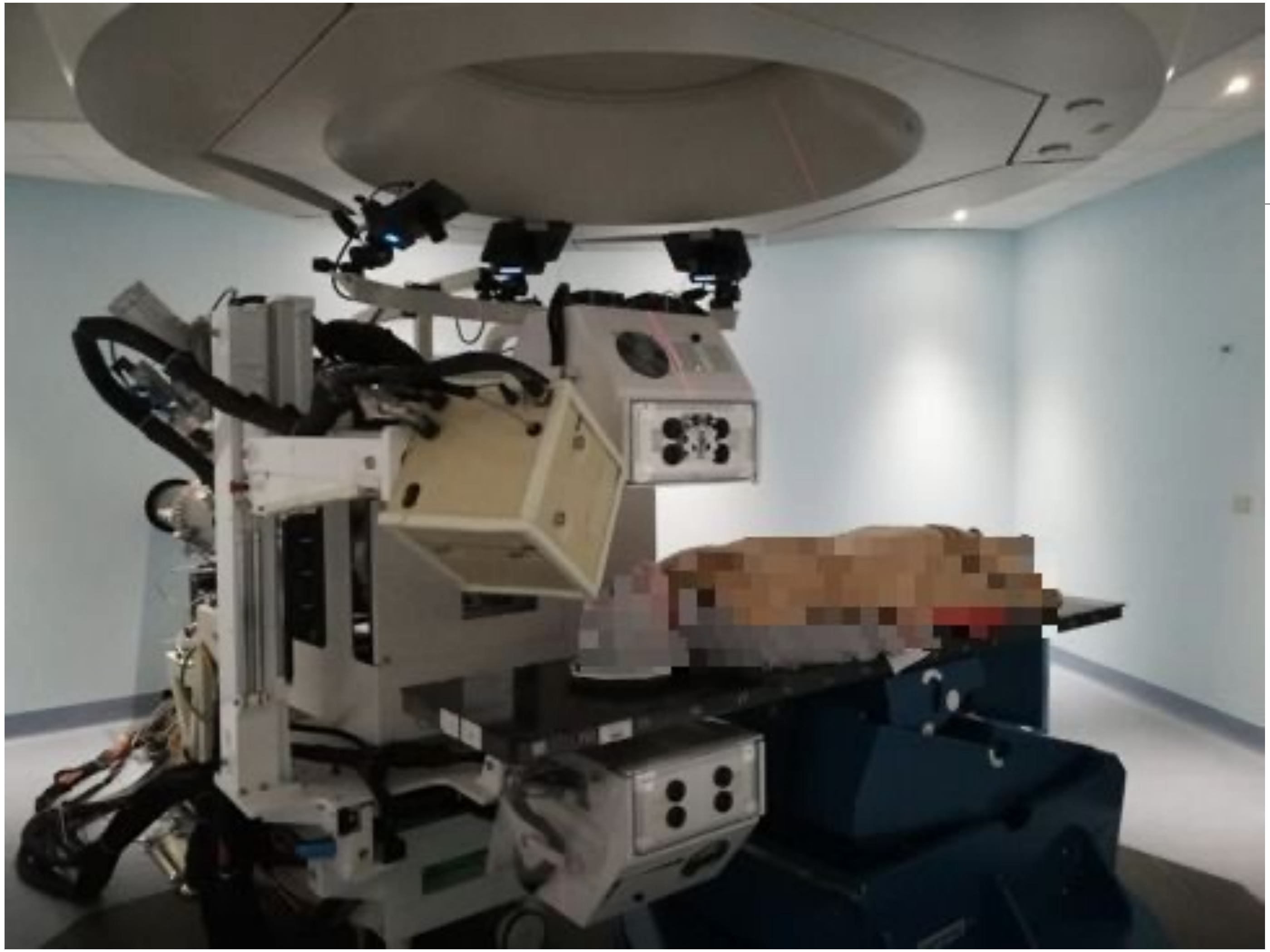
DP planes
orthogonal BCF-12 square scintillating fibres (0.5 x 0.5 x 192 mm^3) read out by SiPMs (1 x 1 mm^2)

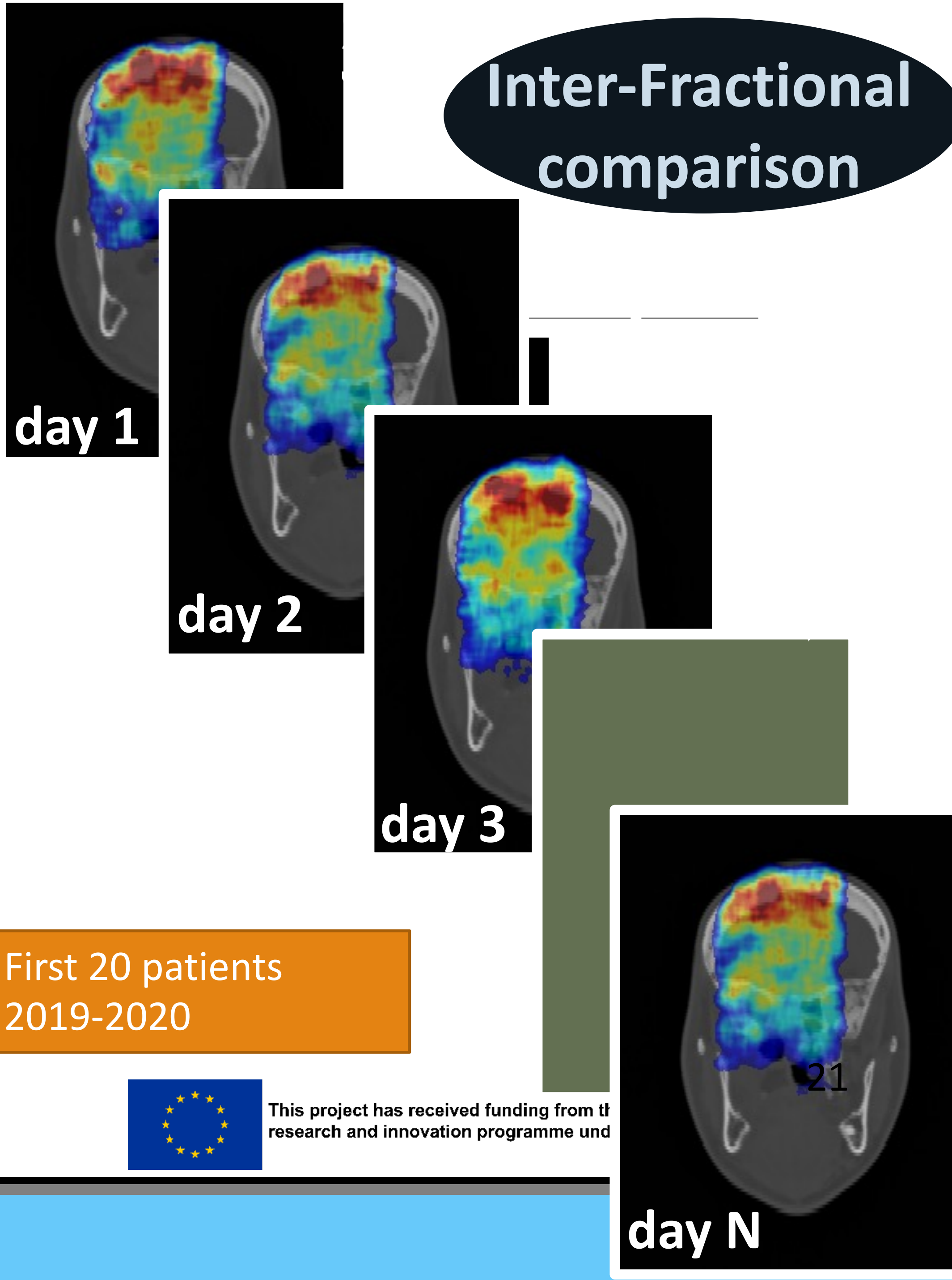
DP box
8 planes
entrance window = 19.2 x 19.2 cm^2
@ 60° wrt the beam direction
@ 50 cm from the isocenter



Main features
Synchronization with Dose Delivery System signal
Image reconstruction method: backtracking with Hough Transform and Point Of Closest Approach

Observational clinical trial





Inter-Fractional comparison

First 20 patients
2019-2020

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ClinicalTrial.gov id: NCT03662373

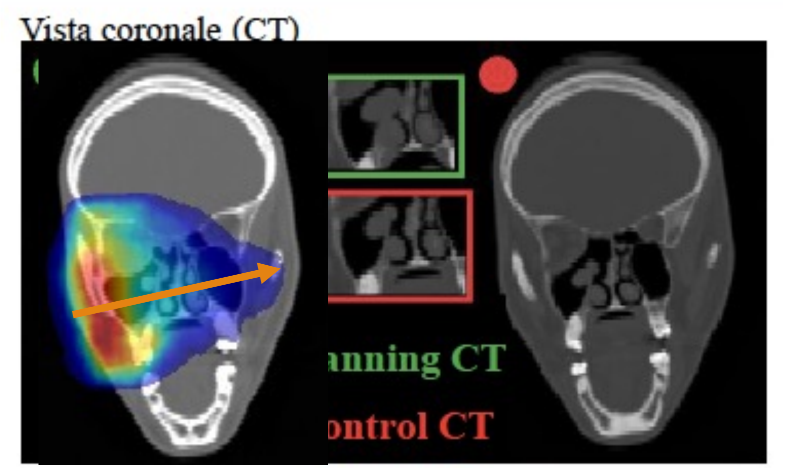
This project has received funding from th
research and innovation programme und

InSide

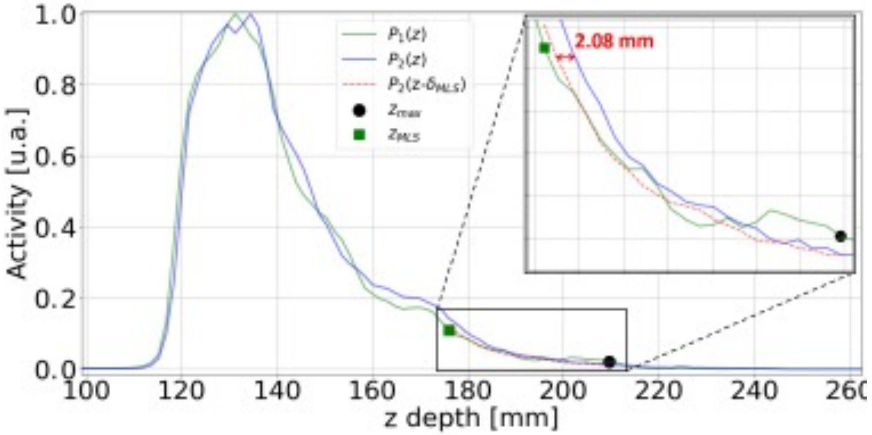
INSIDE: in-beam PET

- ACC (adrenocortical carcinoma) patient

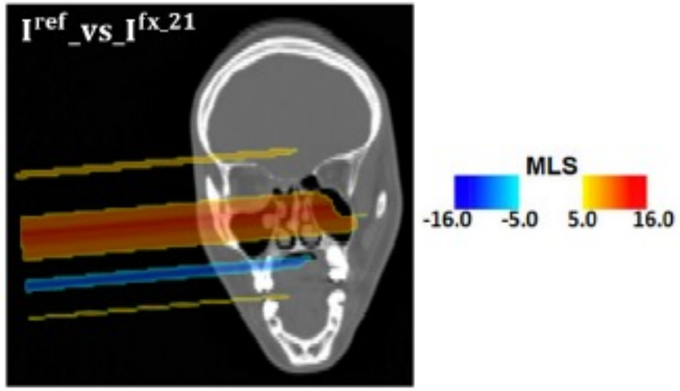
Different range identification methods compared for patient subject to small anatomical changes (BEV, MLS)



E. Fiorina et al,
Front. Phys. 2021



M. Moglioni et al,
Frontiers in Oncology 2022
Accepted for publication



MLS algorithm from Frey K, et al,
Phys. Med.Biol. 59 (2014) 5903–5919

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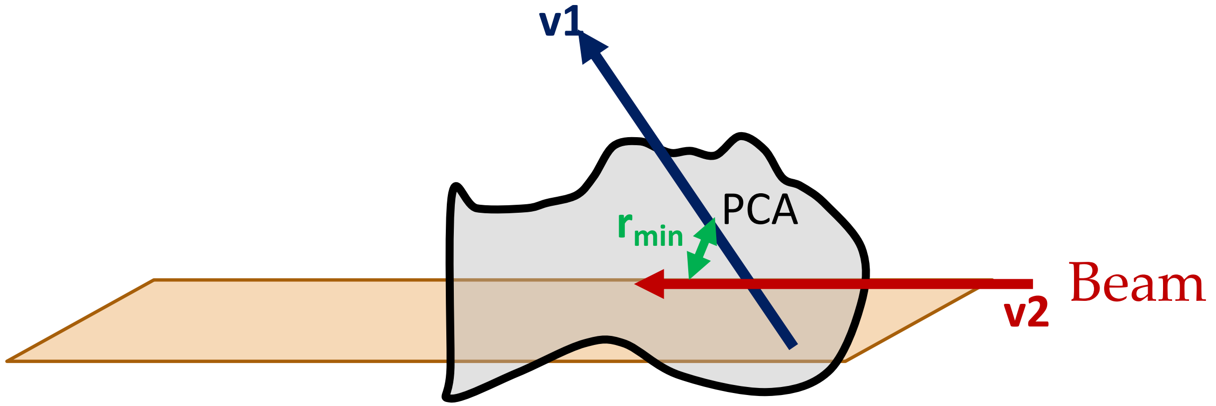
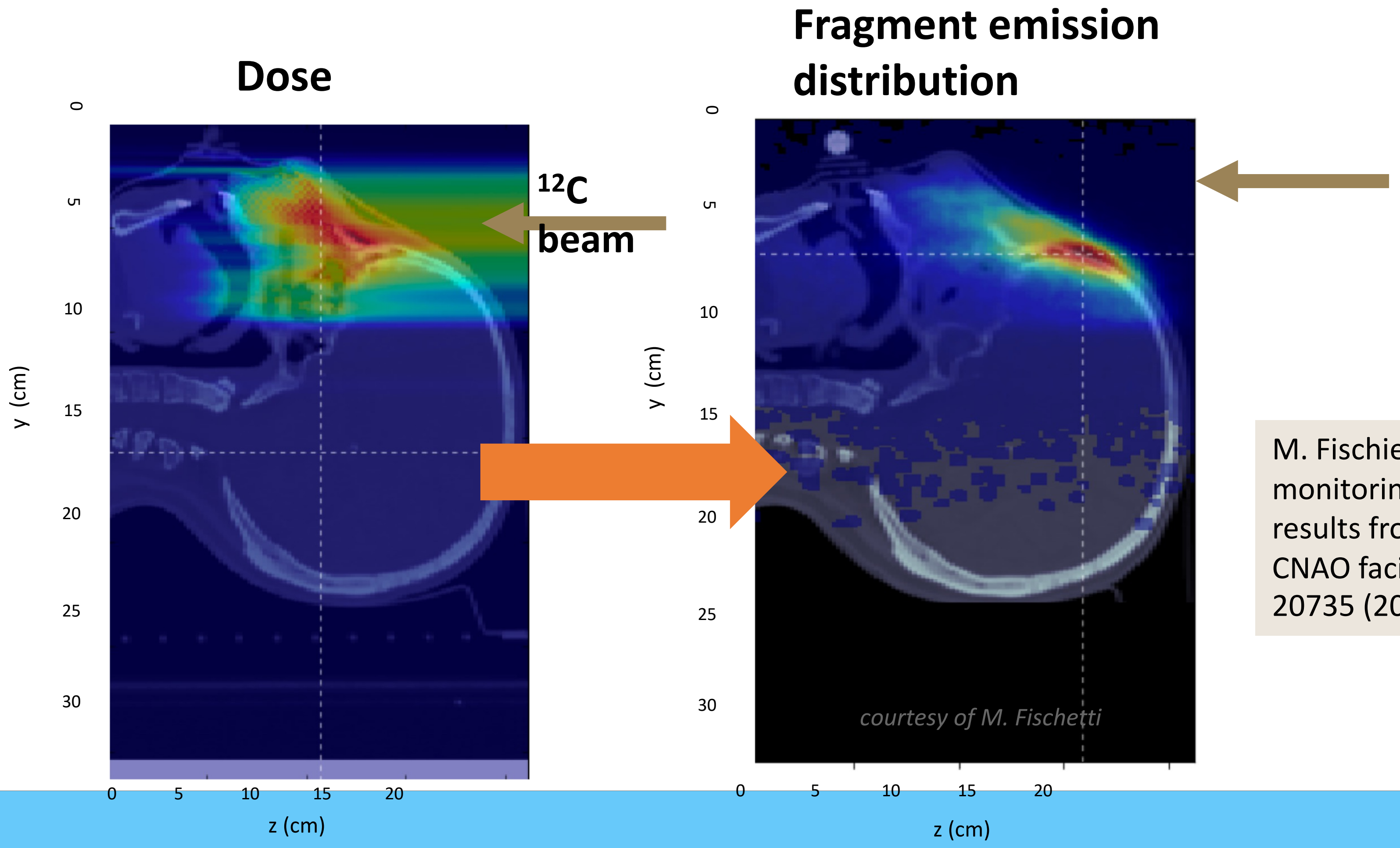
Dose profiler

Production points of the fragments obtained as Points of Closest Approach (PCA) of the reconstructed track with the nominal incoming beam direction



Carbon beam



M. Fischietti et. a., Inter-fractional monitoring of ^{12}C ions treatments: results from a clinical trial at the CNAO facility, Scientific Reports 10, 20735 (2020)

Gamma analysis

Commonly used methods for dose comparisons (measurements versus calculations)

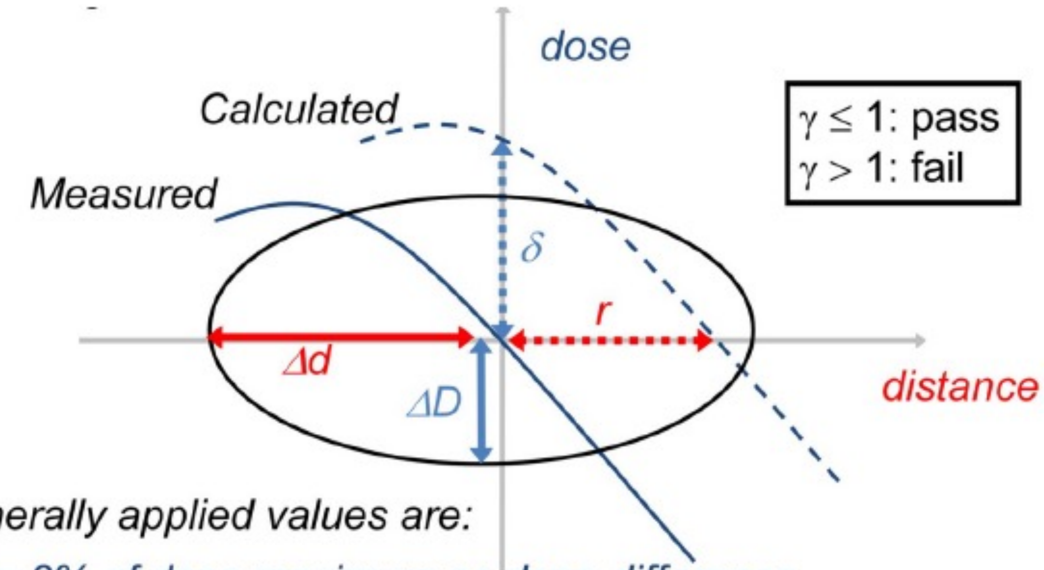
Combines a distance criterion with a dose difference criterion

Original motivation: less sensitive to high-dose-gradient regions than dose difference (and exclude features that are clinically irrelevant)

$$\Gamma(\vec{r_e}, \vec{r_r}) = \sqrt{\frac{|\vec{r_e} - \vec{r_r}|^2}{r^2} + \frac{|D_e(\vec{r_e}) - D_r(\vec{r_r})|^2}{D^2}}$$

$$\gamma(\vec{r_e}) = min\,\{\Gamma(\vec{r_r}, \vec{r_e})\}\ \forall\, \vec{r_r}$$

D.A. Low et al, Med Phys 1998;25(5):656-61.



Generally applied values are:

ΔD = 3% of dose maximum as dose-difference

Δd = 3 mm as distance-to-agreement (DTA)

T=Threshold, often 10% of max dose

Output of the γ-analysis :

- voxilized distribution with γ-values
- Can localize differences
- Can calculate a γ −passing rate (PR) for a given distribution

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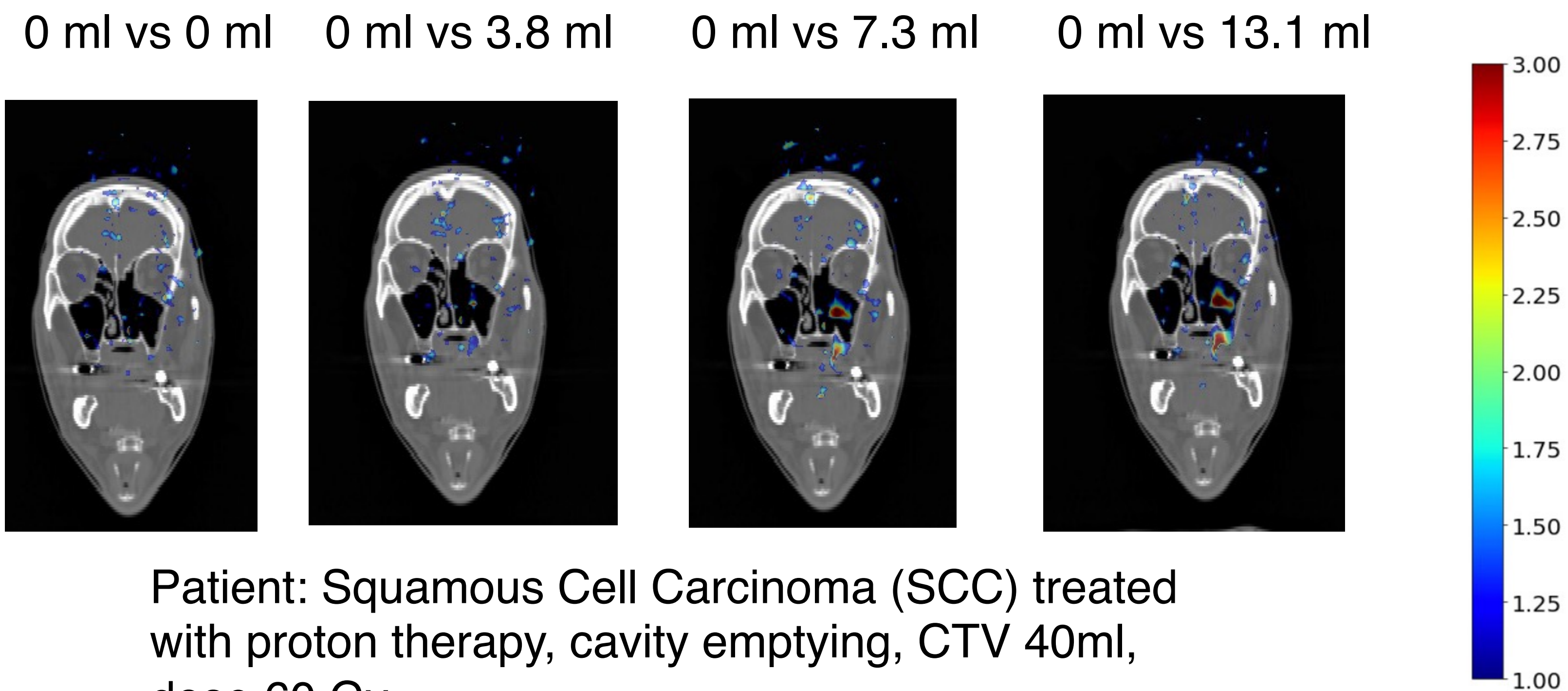
In-beam PET simulations results



Courtesy of A. Kraan
IWORID, June 2022

Gamma index value

Patient: Squamous Cell Carcinoma (SCC) treated with proton therapy, cavity emptying, CTV 40ml, dose 60 Gy

- Treatment and scanner simulated with FLUKA Monte Carlo code
- Image reconstruction with MLEM algorithm

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Results Dose profiler

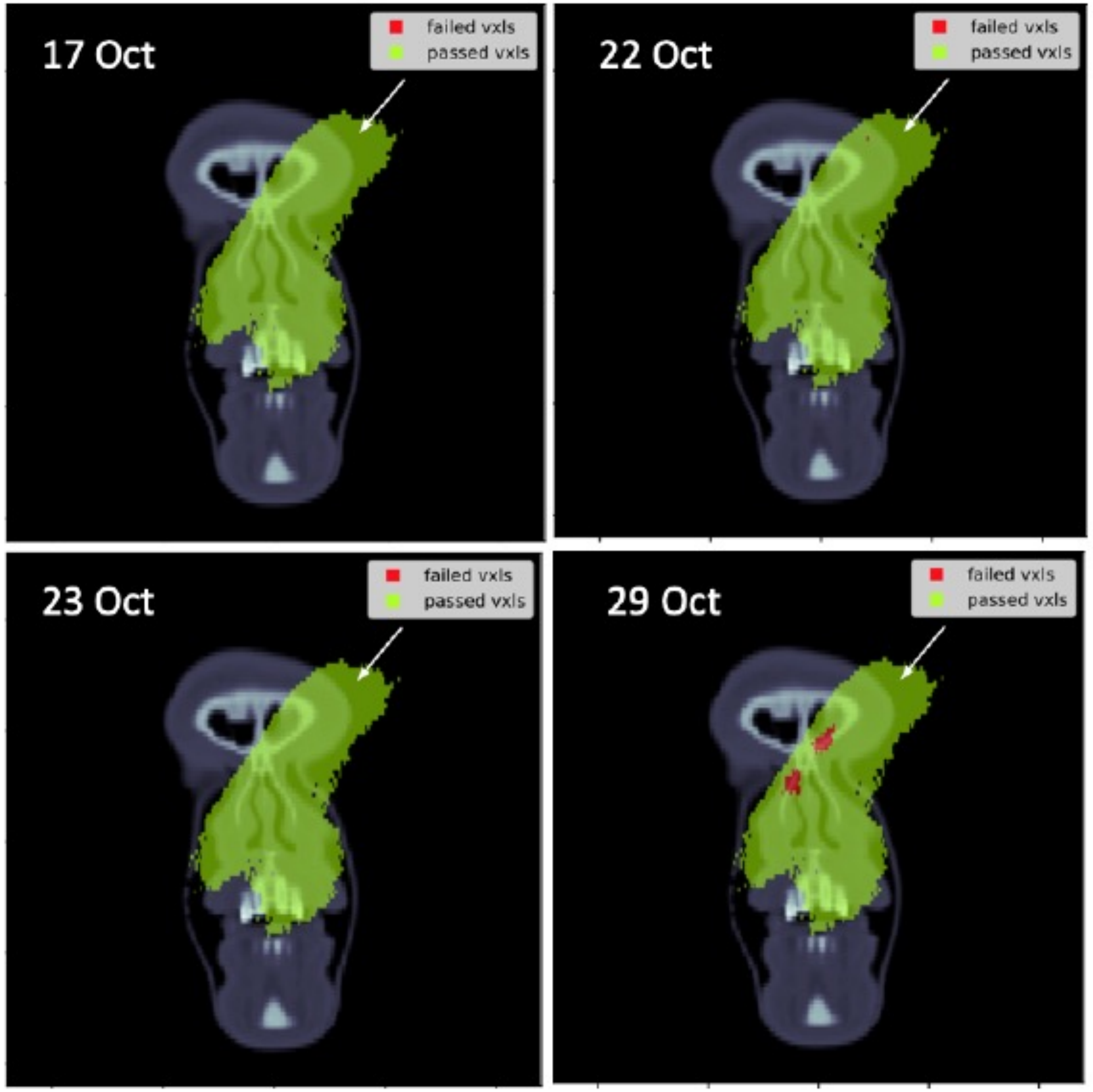
ACC Patient

treated w C ions

Monitored w

Dose porfiler

Gamma analysis
Passing rate



G. Traini et al,
Submitted to
Frontiers in Physics 2022

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roject has received funding from the European Union's Horizon 2020
ch and innovation programme under grant agreement No 101008548

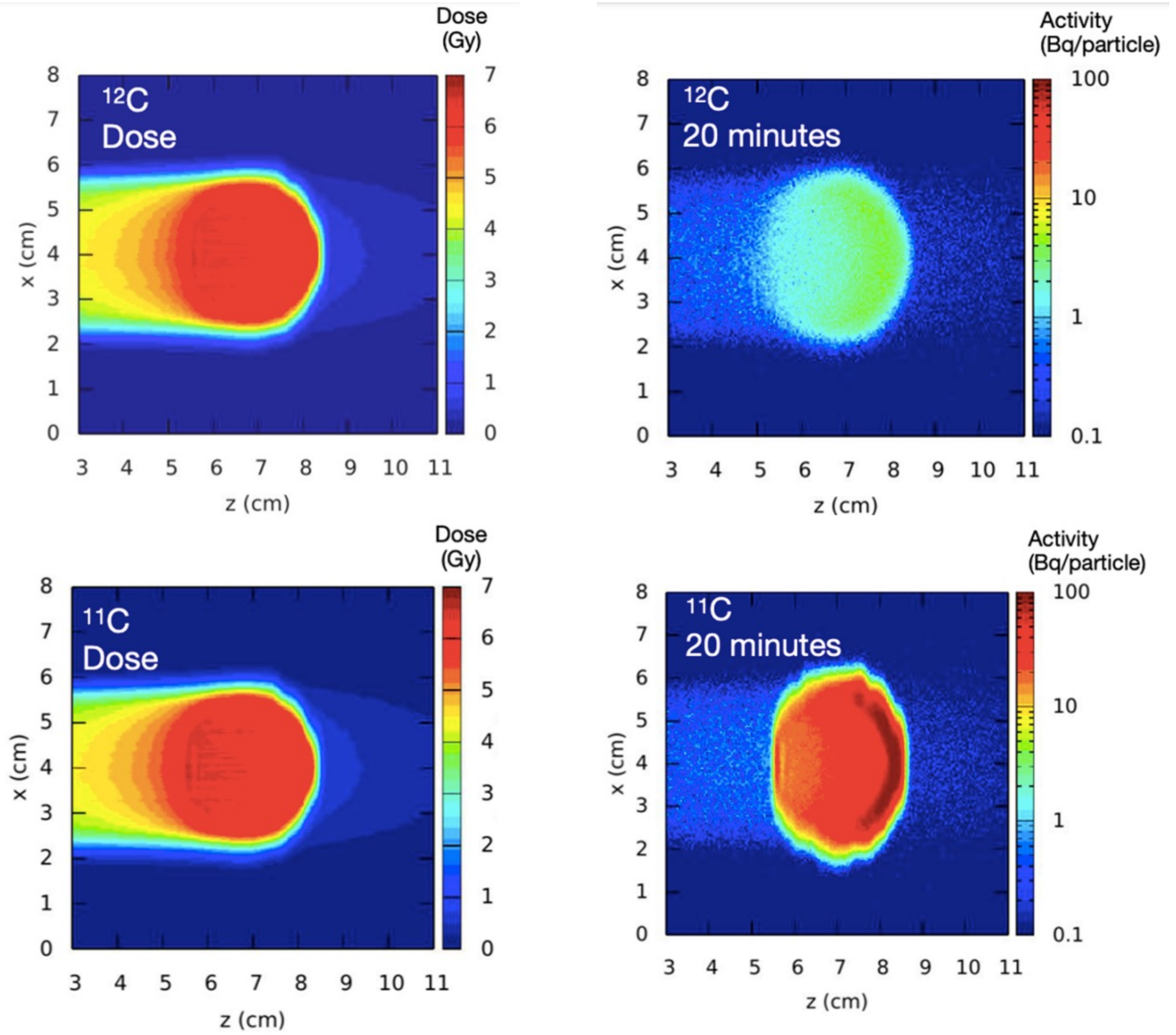
BARB project

(Biomedical Applications of Radioactive ion Beams)

Daria Boscolo et al., Front Oncol 2021. eCollection Radioactive Beams for Image-Guided Particle Therapy: The BARB Experiment at GSI

- FAIR project Darmstadt
- Carbon beams: not much beta+ activity generated…
- But higher intensity for the PET signal can be obtained using beta+ -radioactive beams directly for treatment
- Difficult (low intensity)

- Intensity upgrade of the SIS-18 synchrotron and improved isotopic separation at FAIR (Facility for Antiproton and Ion Research at GSI) → now possible to reach radioactive ion beams with sufficient intensity to treat a tumor in small animals
- ^{11}C and ^{15}O beams



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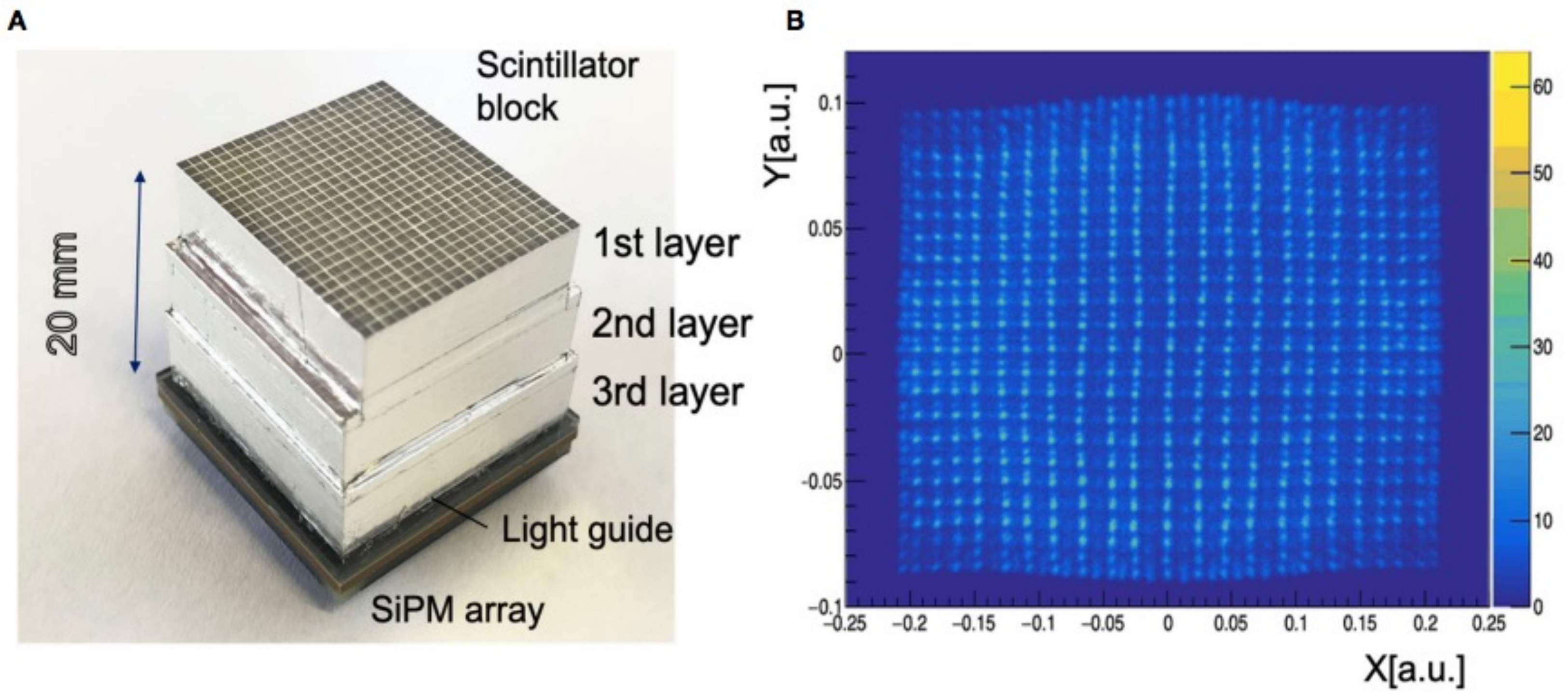


FIGURE 6 | LMU hybrid γ-PET detector **(A)** A 3-layer PET detector developed at LMU Munich in collaboration with NIRS-QST. The PET detector consists of a 3-layer scintillator block, a light guide and an 8 × 8 SiPM array. **(B)** A flood map of the 3-layer PET detector exposed to a ^{22}Na radioactive point source.

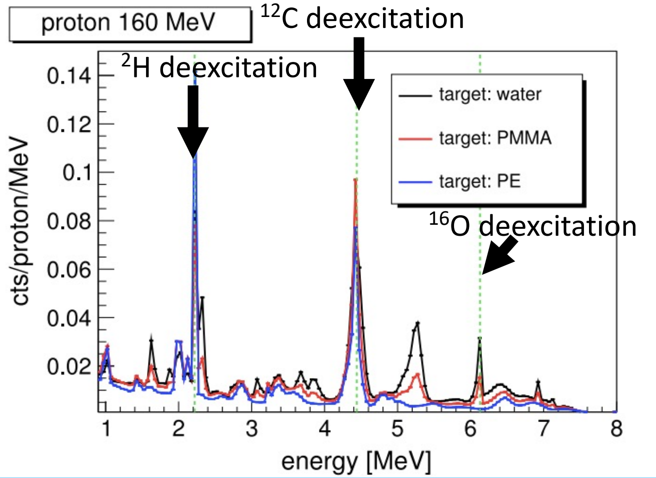
European Union's Horizon 2020
r grant agreement No 101008548

Prompt gamma

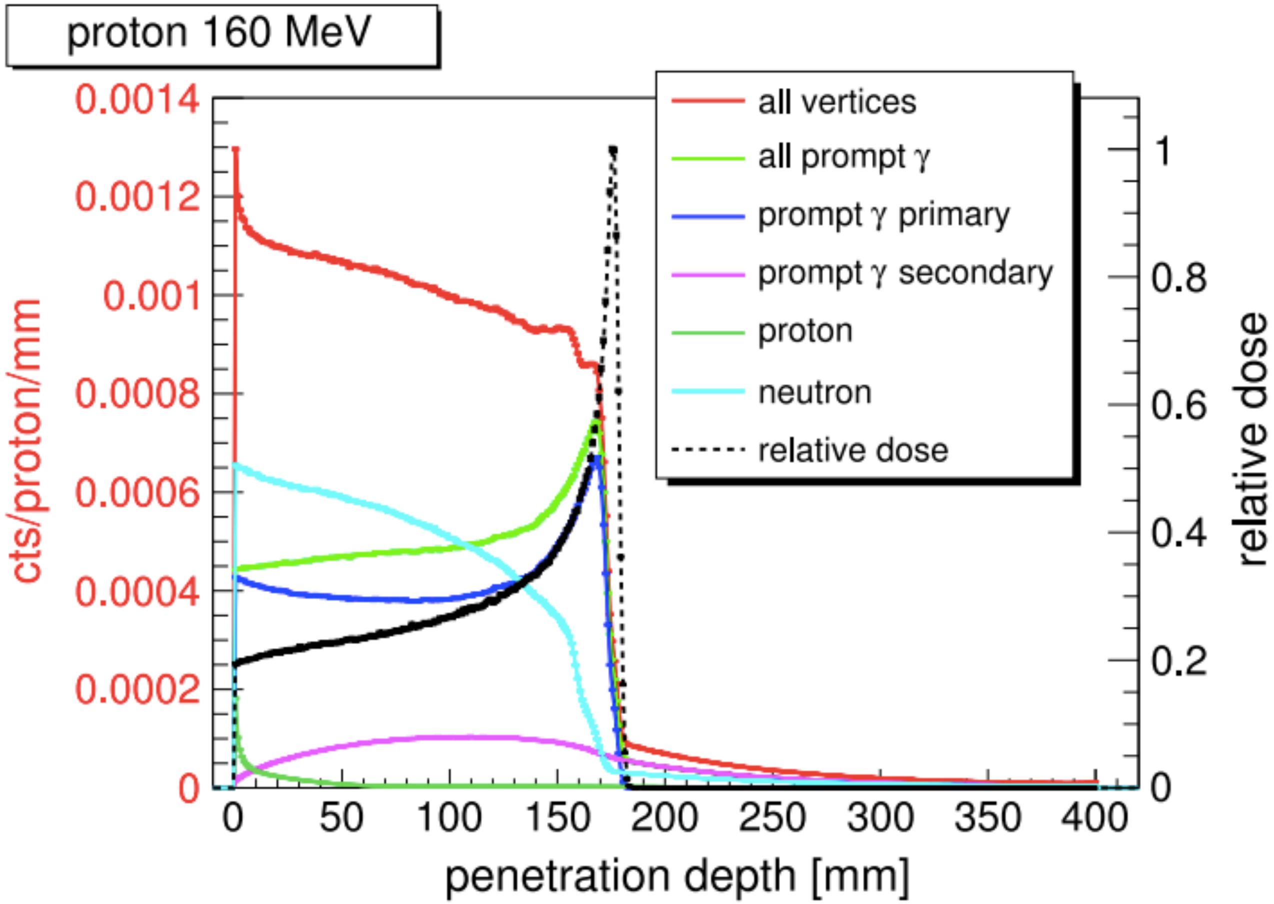
First proposed in 2003 by Stichelbaut and Jongen, first prototype by Min in 2006

Difficulties with detecting prompt gamma's:

- Broad energy spectrum (up to 10 MeV!!)
- Large background (neutrons)
- High instantaneous count rates
- Compatibility constraints with patient irradiation.



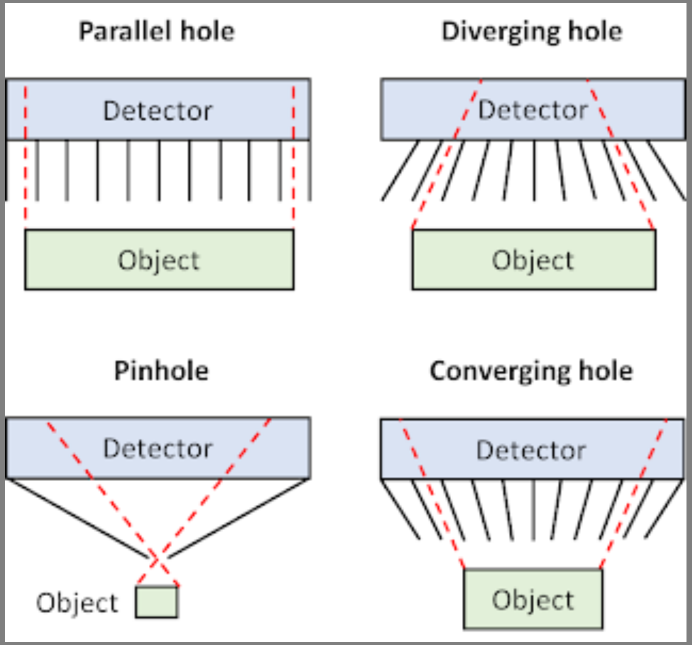
J.Krimmer, D.Dauvergne, J.M.Létang, É.Testa, Prompt-gamma monitoring in hadrontherapy: A review, NIM A 878, 2018, pp 58-73



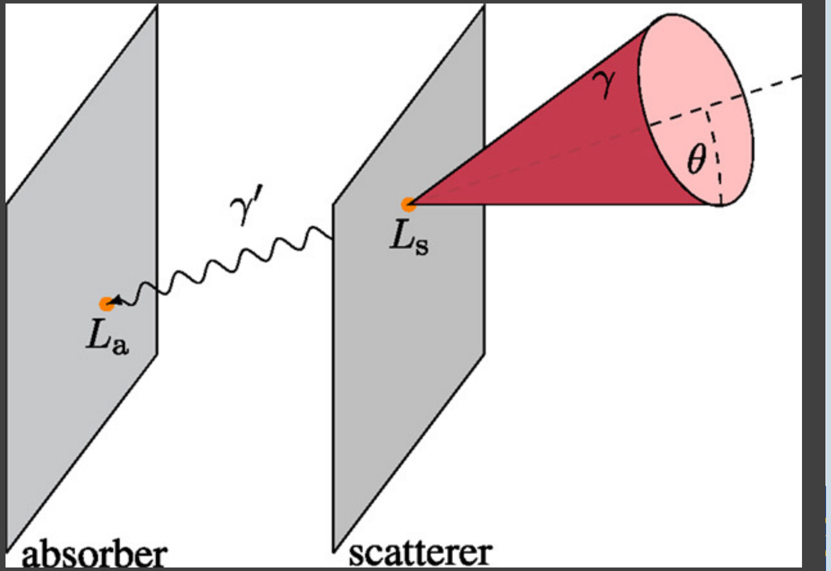
Prompt gamma

See for information and references: J.Krimmer, D.Dauvergne, J.M.Létang, É.Testa, Prompt-gamma monitoring in hadrontherapy: A review, NIM A 878, 2018, pp 58-73

Collimated gamma cameras

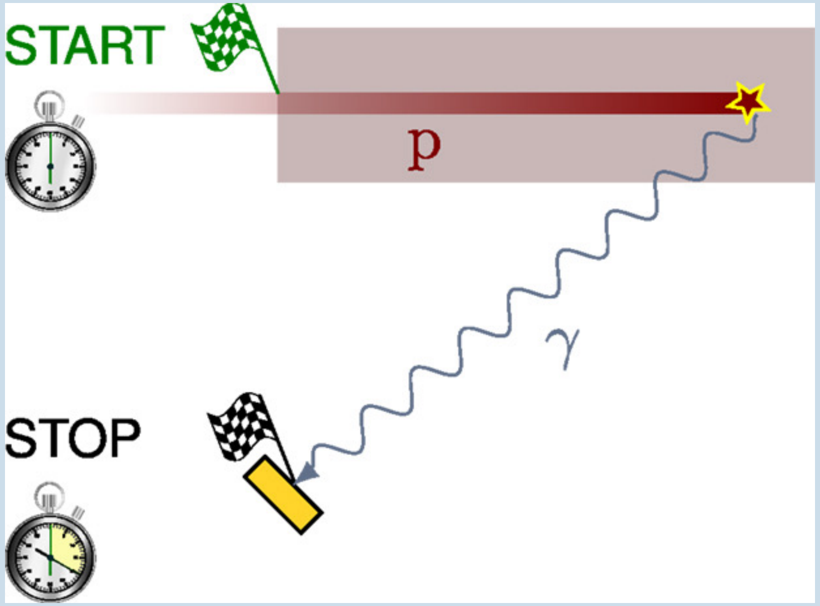


Compton cameras



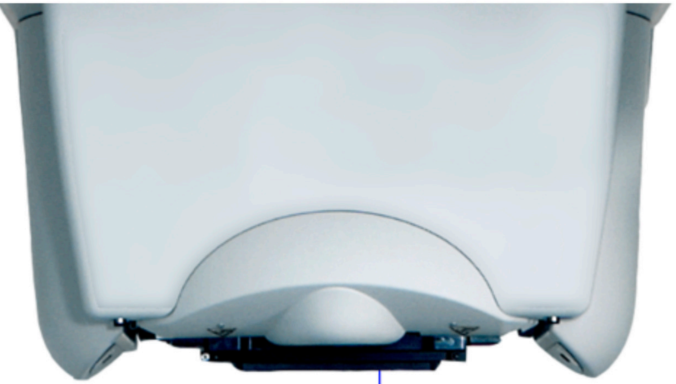
From F. Hueso-González, Front. Oncol., 2016

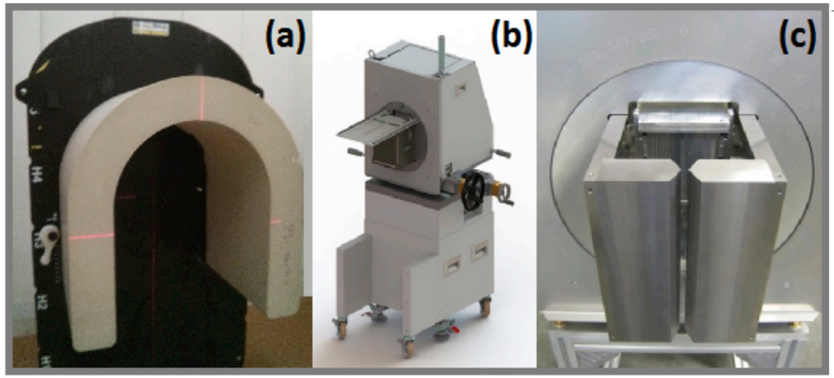
Others, for instance timing



From F. Hueso-González, Front. Oncol., 2016

Prompt gamma

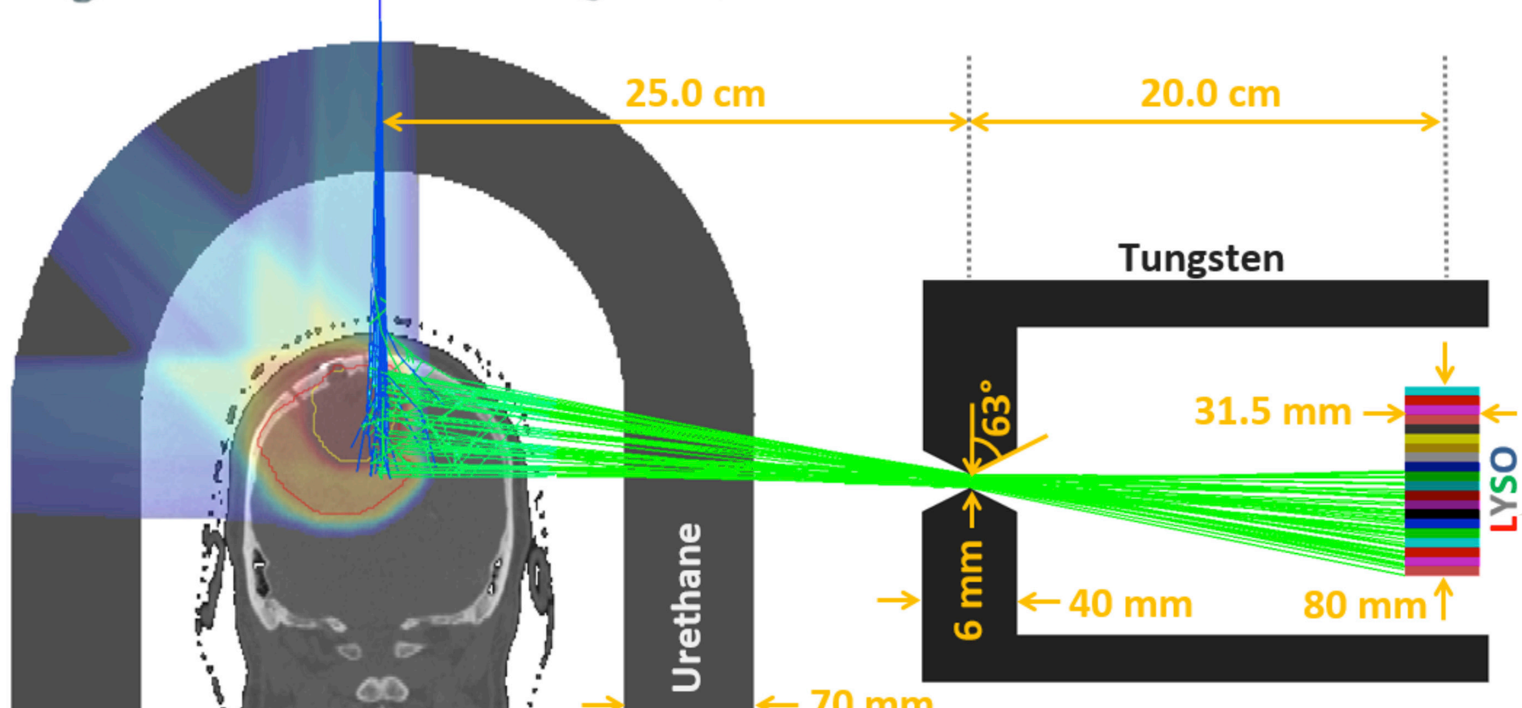




Example of clinical applications of **collimated gamma** imaging systems:

IBA-USA collaboration: report 2 mm precision to detect shift

Yunhe Xie et al , Prompt Gamma Imaging for In Vivo Range Verification of Pencil Beam Scanning Proton Therapy Int. J. Rad. Onc. Bio. Phys. 99, 1, 2017, pp 210-218



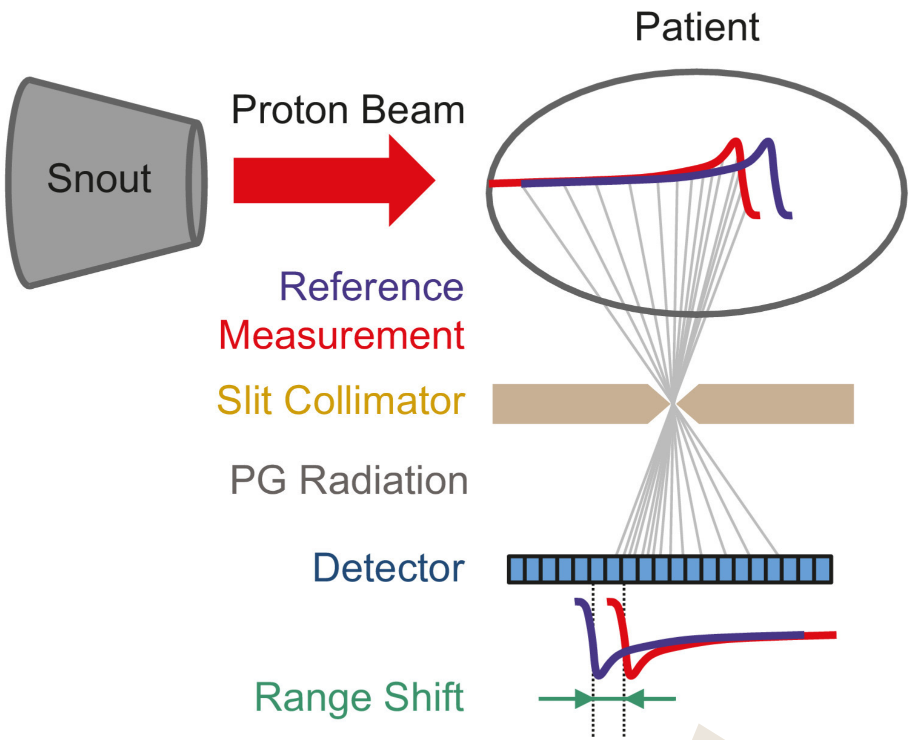
Reversed projection of the prompt gamma depth emission profile is produced on the crystals

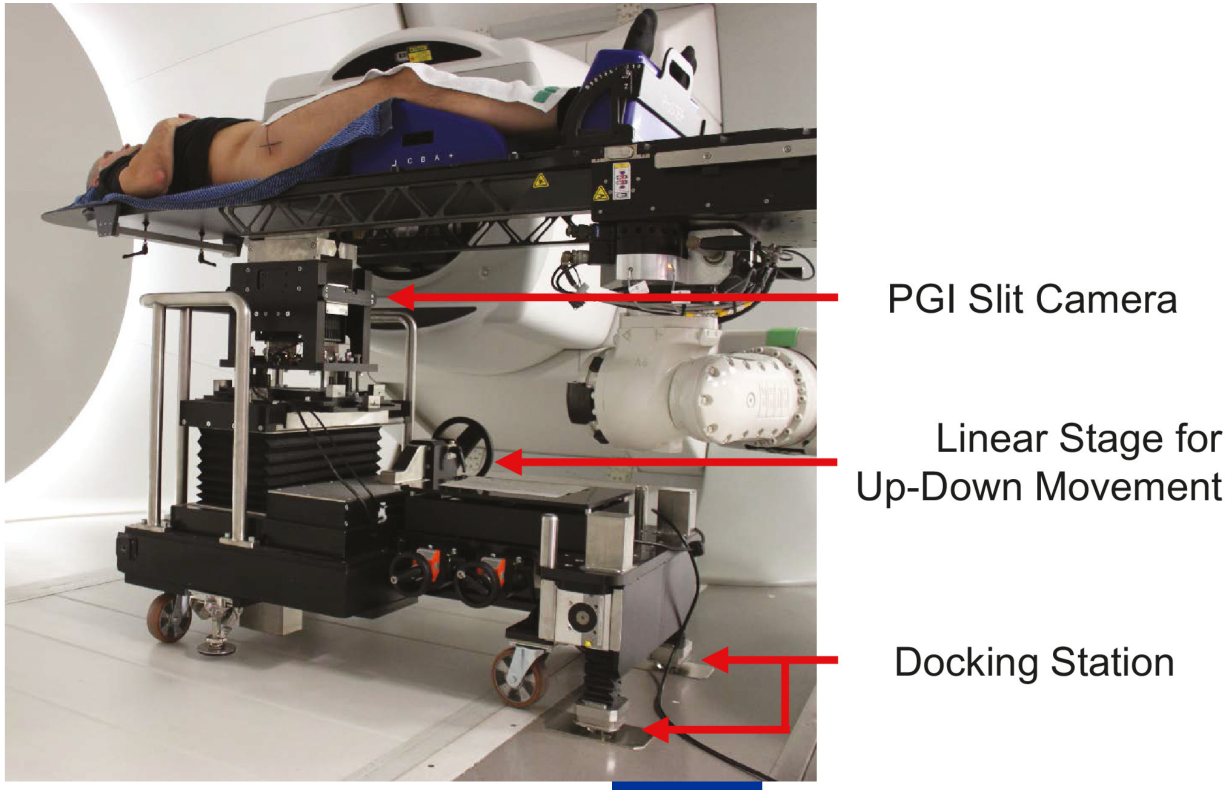
m the European Union's Horizon 2020
under grant agreement No 101008548

Prompt gamma

Other example of clinical applications of **collimated gamma** imaging systems:

J. Berthold et al, Int. J. Rad. Onc. Bio. Phys. 111, 4, **15 November 2021**, Pages 1033-1043





n Union's Horizon 2020
reement No 101008548

Reversed projection

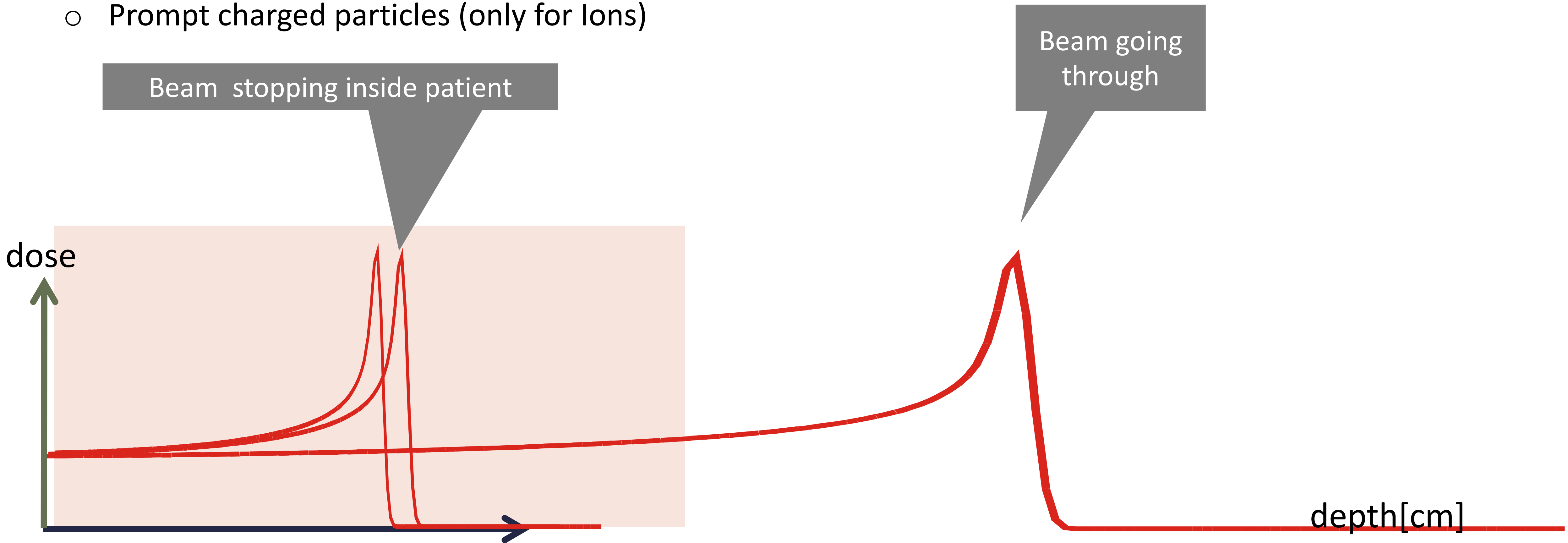
validation uncertainty of this second-generation PGI slit camera is about 1 mm (2σ)

Proton CT (pCT)

Based on Nuclear Reactions of Hadrons in Tissue

- Off-line & On-line PET
- Prompt gamma’s and neutrons
- Prompt charged particles (only for Ions)

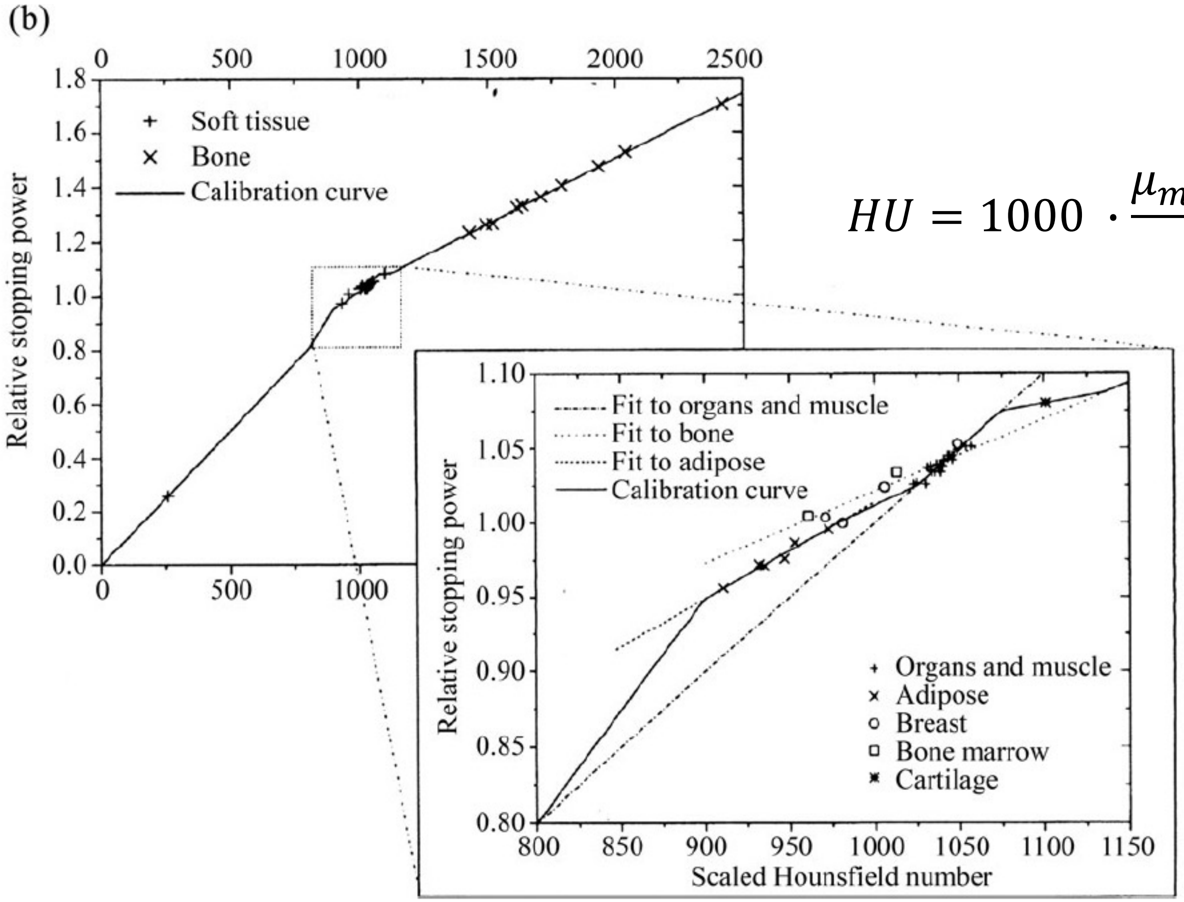
Based on X-ray CT- analogous: pCT (only for Protons)



Proton CT: motivation

- Proton range depends on stopping power along the proton path.
- Currently stopping power determined by CT scan (x-Ray based)
- CT Hounsfield units have to be converted to particle stopping power… based on calibration curves → uncertainties!

  - Can be improved…
    - Dual energy CT
    - Proton CT (see next)
    - …



$$HU = 1000 \cdot \frac{\mu_m - \mu_w}{\mu_w}$$

ICRU, 2007

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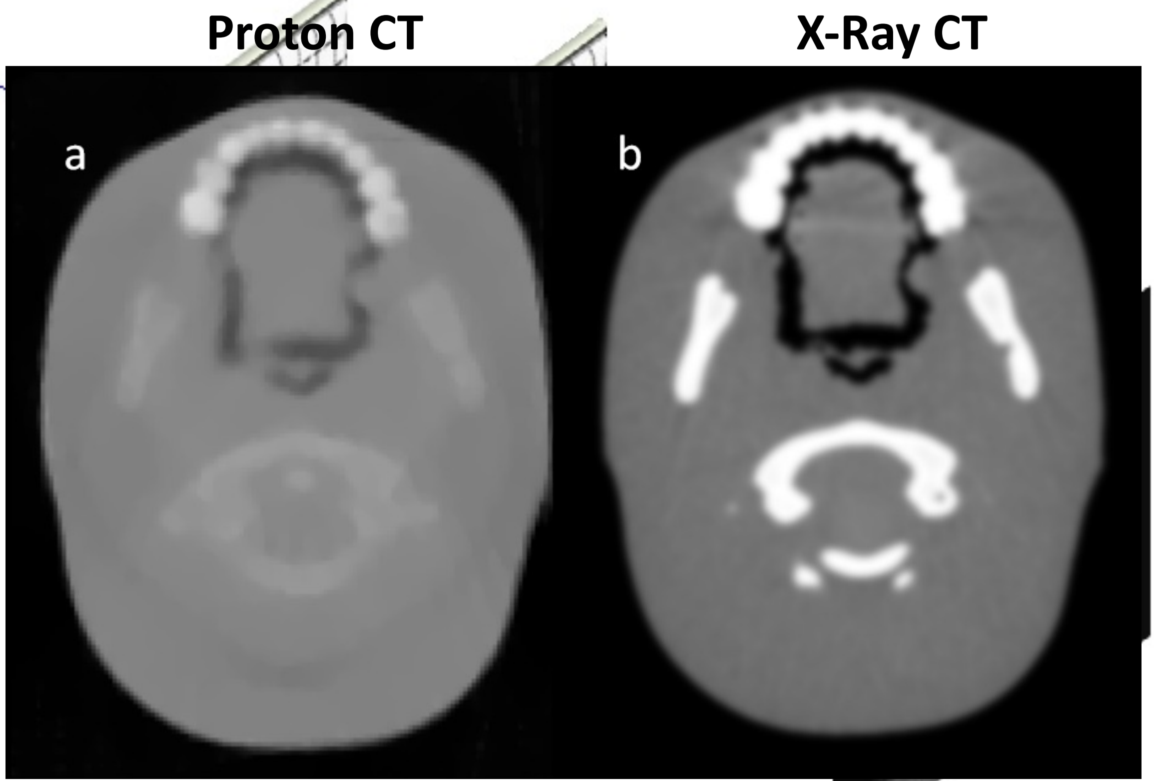
Proton CT

Using same particles (i.e. protons) but with higher energy, so that they pass through the target:

- Measure the position with a tracker before and after the target
- Measure the residual energy with an energy detector (calorimeter) downstream
- Make one planar view to obtain a proton-radiography (pR)
- Source of image contrast in a proton radiograph is the energy loss of the transmitted protons (the integrated stopping powers of protons in the patient).
- Make many projections to obtain a proton-CT (pCT)
- Idea was originally proposed by Allan Cormack in 1963 (J.Appl. Phys.1963,34, p.2722)

Robert P Johnson,
Review of medical radiography and tomography with proton beams
Rep. Prog. Phys. 81 (2018) 016701 (21pp)

https://www.niu.edu/crcd/prospective-user/projects/proton-medical-imaging.shtml



R.P. Johnson et al. A fast experimental scanner for proton CT: technical performance and first experience with phantom scans. IEEE Trans. Nucl. Sci., 63:52, 2016.

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Conclusions

- Many applications of detectors and instrumentation in particle therapy
- Imaging is used during all stages of particle therapy
- Today discussed a few of the techniques, focusing on techniques used for treatment monitoring

Thank you for your attention

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Aknowledgments

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Marco Schwarz, Radiation Oncology Dep. University of Washington, Seattle, USA
Mario Ciocca, CNAO, IT

Collaboration INnovative Solutions for In-beam DosimEtry in Hadrontherapy

N. Belcari, N. Camarlinghi, A. Del Guerra, S. Ferretti, E. Kostara, A. Kraan, B. Liu
N. Marino, M. Morrocchi, M.A. Piliero, G. Pirrone, V. Rosso, G. Sportelli

P. Cerello, S. Coli, E. Fiorina, G. Giraudo, F. Pennazio
C. Peroni, A. Rivetti, R. Wheadon, A. Attili, S. Giordanengo

E. De Lucia, R. Faccini, P.M. Frallicciardi, M. Marafini, C. Morone
V. Patera, L. Piersanti, A. Sarti, A. Sciubba, C. Voena

F. Ciciriello, F. Corsi, F. Licciulli, C. Marzocca, G. Matarrese

G. Battistoni, M. Cecchetti, F. Cappucci, S. Muraro, P. Sala

CNAO: Mario Ciocca, Sandro Rossi, Viviana Vitolo, Esther Orlandi, Sara Tampellini, Marco Pullia

Back up

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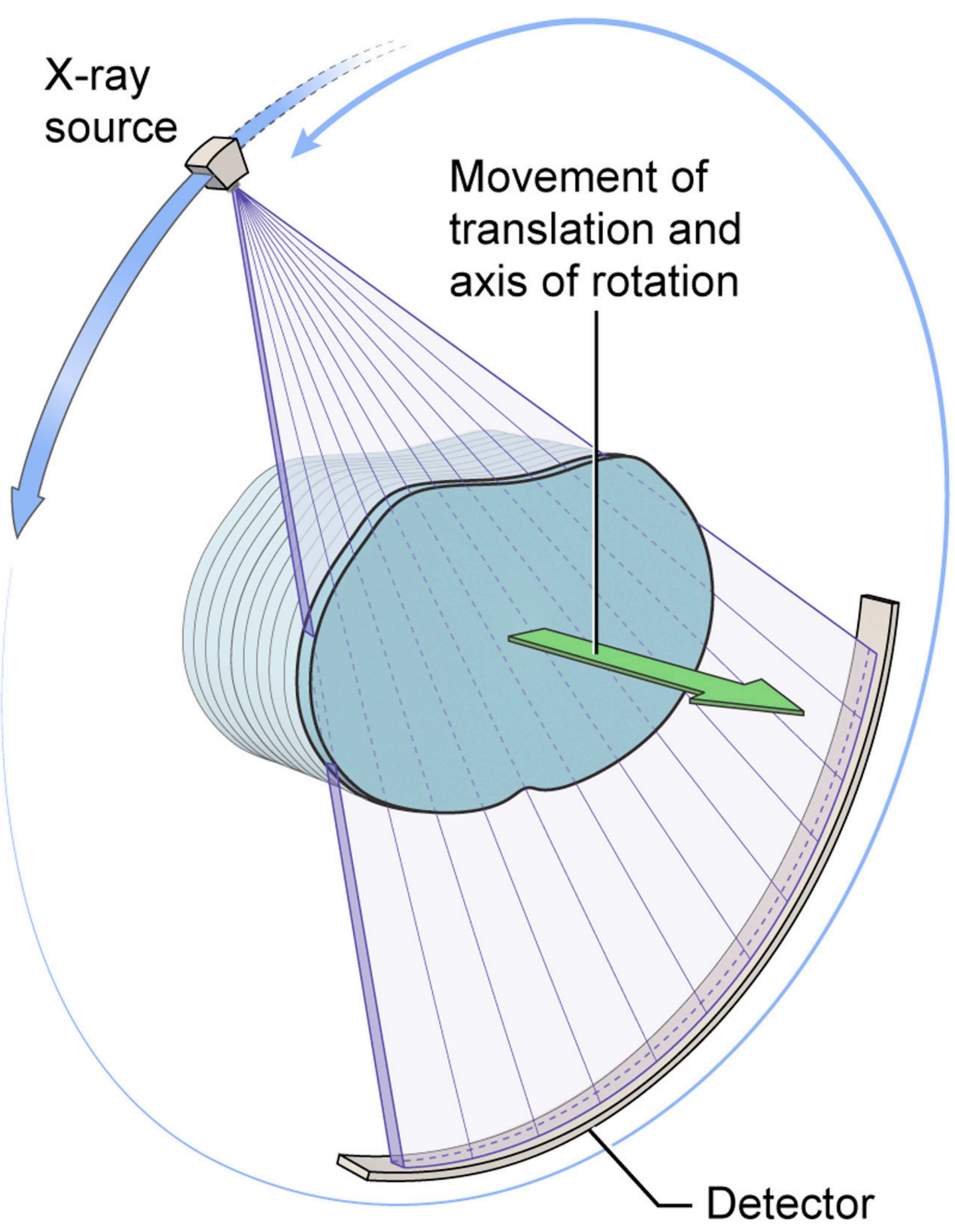
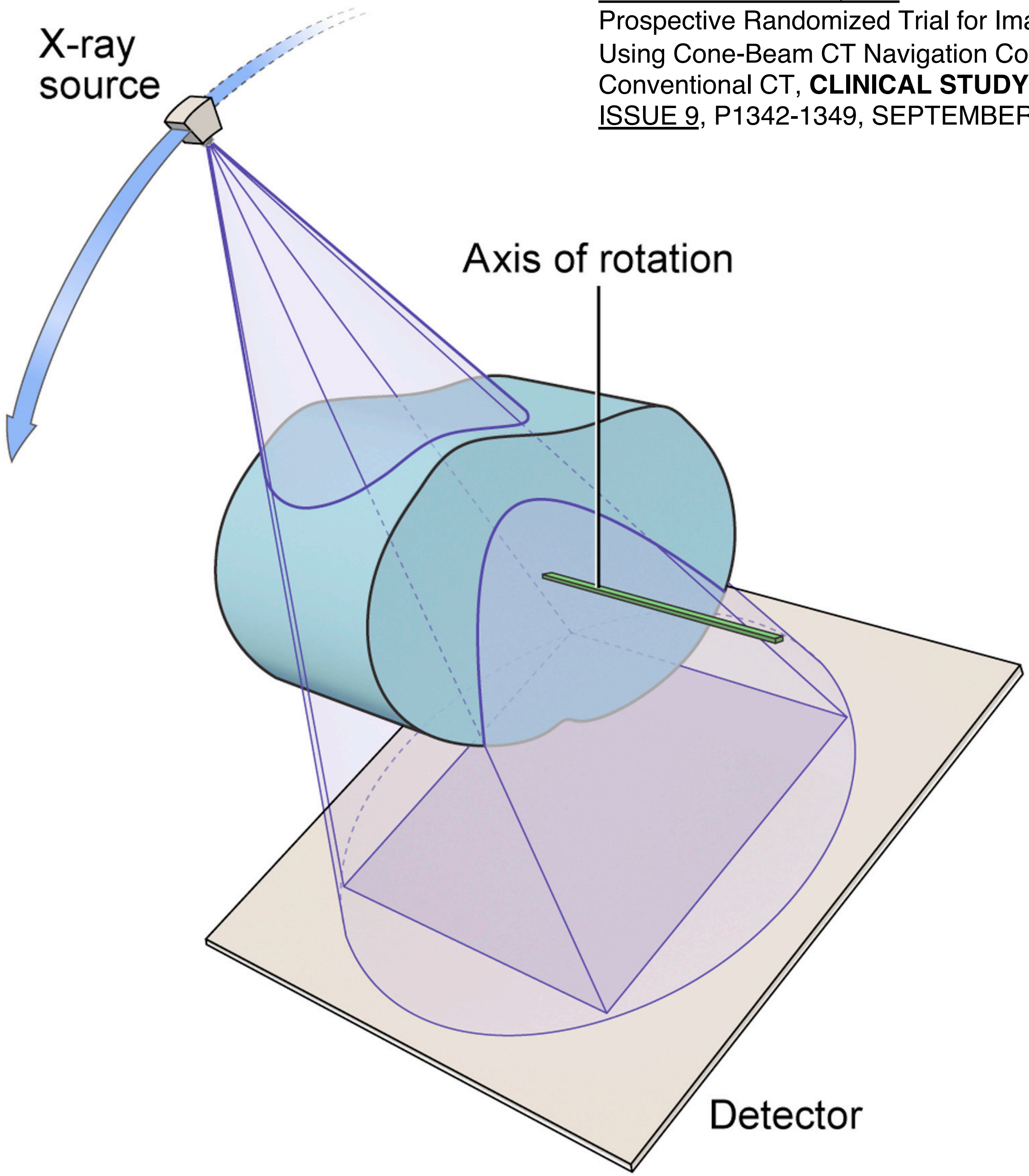
CT

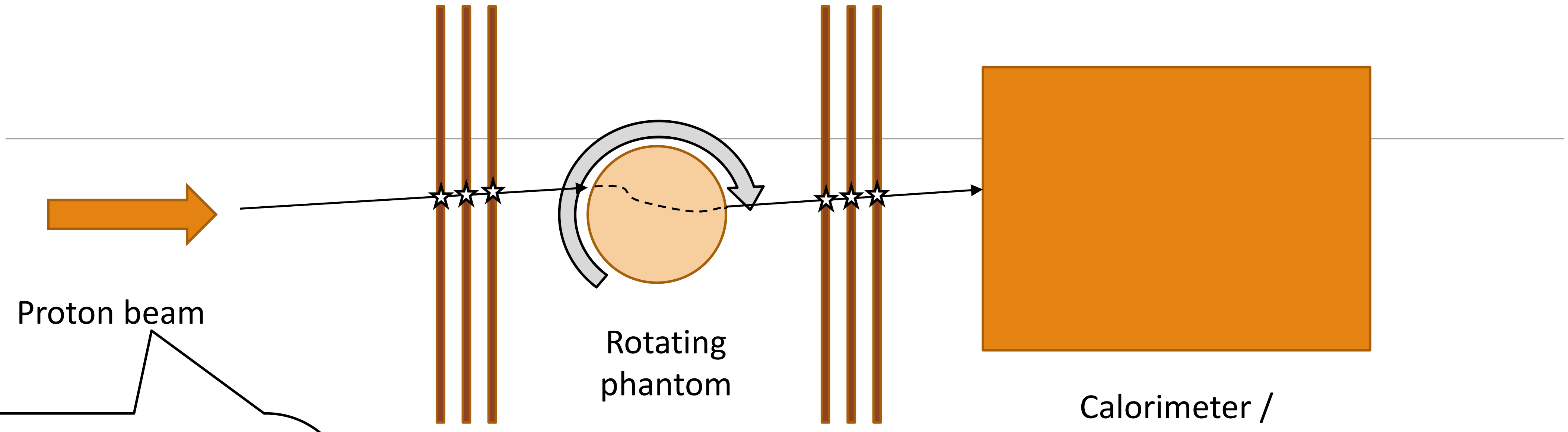


CBCT



Nadine Abi-Jaoudeh, MD
Prospective Randomized Trial for Image-Guided Bi
Using Cone-Beam CT Navigation Compared with
Conventional CT, **CLINICAL STUDY**| VOLUME 27
ISSUE 9, P1342-1349, SEPTEMBER 01, 2016

Structure of a Proton CT system



Energy should be high enough to pass the phantom.

- Higher energy → less multiple scatter contribution
- Lower energy → higher water equivalent path length resolution

The used value is usually the maximum energy available in the treatment facility

Measures position and direction before and after the phantom to estimate the «most likely path». Due to multiple scattering the path cannot be assumed linear in the phantom.

Measures the residual energy of the proton, usually expressed as «Water Equivalent Path Length». The measurement can be performed usign a scintillator calorimeter, a MultiLayer Ionization Chamber, or a Time of Flight system.