In-vivo patient treatment verification with in-beam PET at the National Center for Oncological Hadron-therapy:

inter-fractional data analysis using the gamma evaluation method

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Outline

- Introduction:
  - Proton therapy
  - Treatment monitoring with Positron-Emission-Tomography
- Methods and materials:
  - INSIDE PET system at CNAO
  - Inter-fractional PET image comparison
- Results:
  - Gamma analysis applied on MC simulations
  - Gamma analysis applied on a real patient
- Conclusions

Cancer treatment

Surgery
Removal of cancer cells using surgery

Radiotherapy
Destruction of cancer cells using radiation

Chemotherapy
Destruction of cancer cells using drugs (anti-cancer agents)

- In Italy 373.000 new cases/year
- More than 50% of all patients receive radiotherapy along treatment
- Most treatments with photons
- Last decades: growing interest in particle therapy, mostly
  - Protons
  - Carbon ions
- 3 centers: Catania, Pavia (CNAO), Trento

From: http://www.salute.gov.it

Proton therapy

Compared to photons, protons have a more selective energy deposition

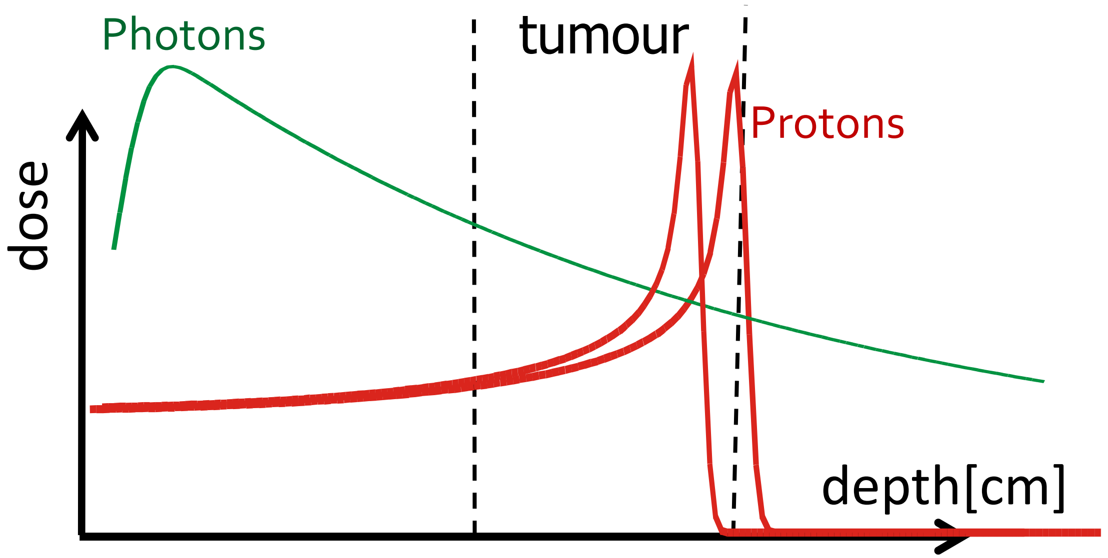
Photons : high dose delivered in front and behind tumor

Protons : Bragg Peak
- Nr of particles → height
- Energy→ depth

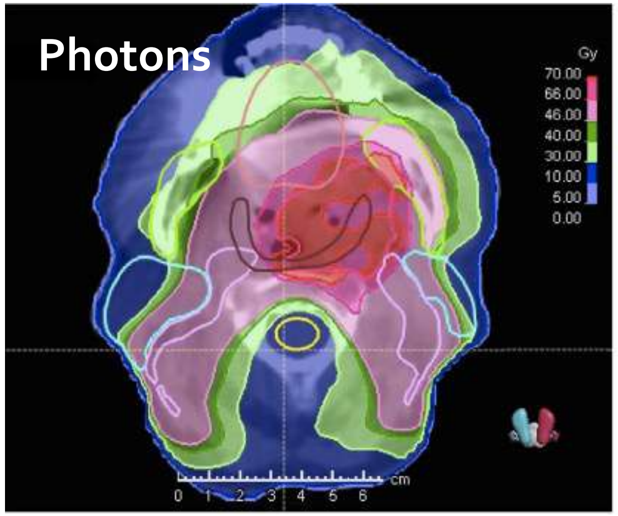
→More conformal dose!

Intensity Modulated Proton Therapy: combining thousands of beams

Treatment typically takes 4-6 weeks (20-30 treatment **fractions**)



From: A. Beddok et. al., Radiotherapy and Oncology 147 (2020) 30–39



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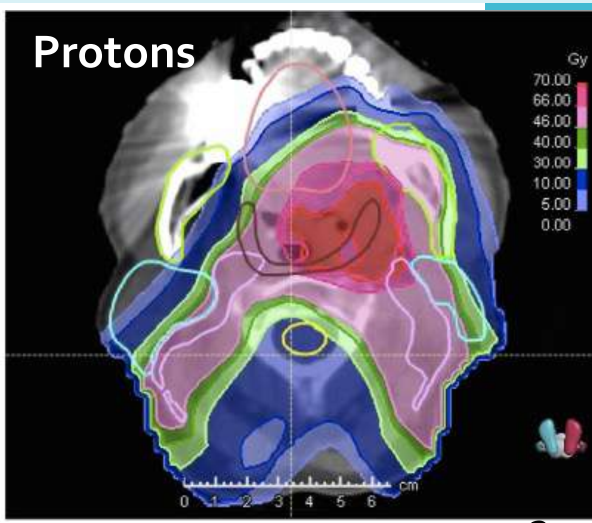


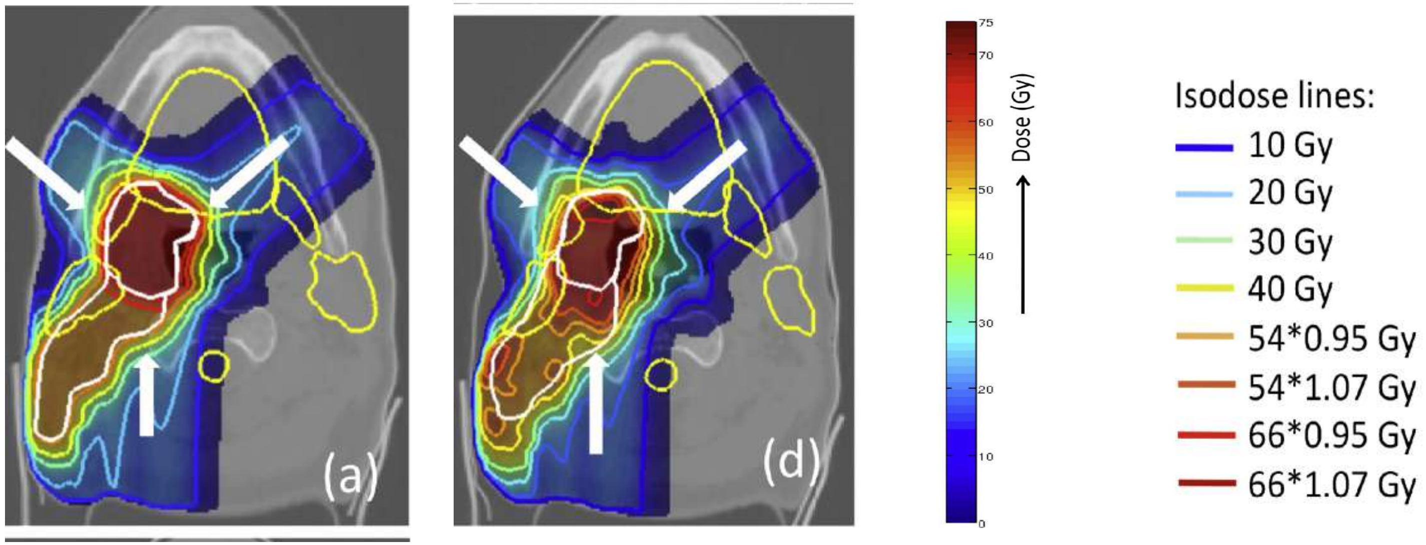
Proton therapy

Topical Review: Adaptive proton therapy
H. Paganetti, P. Botas, G. C. Sharp, B. Winey 2021, Phys. Med. Biol.66, 22

- Proton therapy is accurate but also sensitive to uncertainties…
- Among sources of uncertainties are anatomical changes → dose distortions
- Example of site where this can be problematic: head and neck tumors
- Often a control CT scan is made after X treatments, with X depending on clinical experience/personal choice of the radiation oncologist → adapt treatment?
- Treatment should be monitored!
  - For patients who change: to be sure to perform the control CT in time → adapt
  - For patients who do not change: to avoid unnecessary control CT's

start after 3 weeks

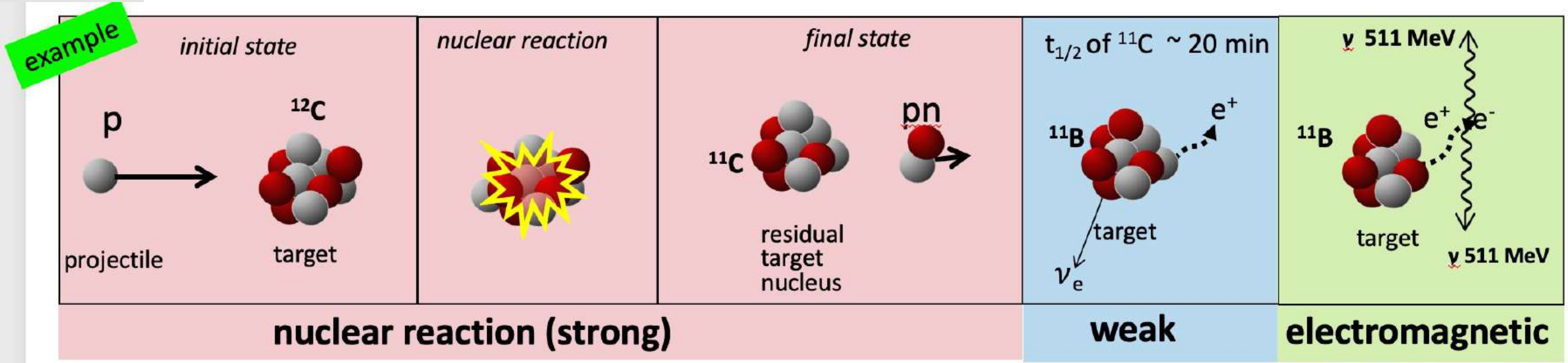
From Kraan et al Int J Radiat Oncol Biol Phys 2013;87(5):888-96.



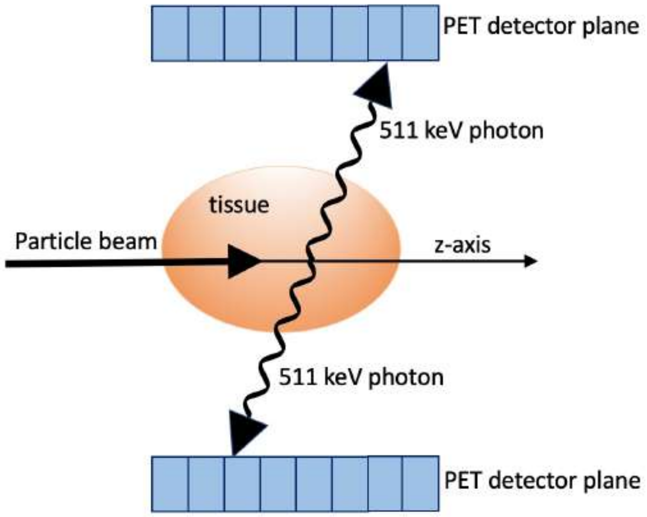
PET Treatment monitoring

Enghardt W, Parodi K, et al. *Radiother Oncol* (2004)

- Can make use of nuclear interaction



- Among nuclear fragments produced are β^+ emitters
- Positron Emission Tomography (PET) can be used for in-vivo non-invasive treatment monitoring in proton therapy



See:

- K. Parodi, J. C Polf, Review: In vivo range verification in particle therapy, Med Phys 2018 45(11)
- M. Durante, H. Paganetti, Re.p Prog. Phys. 2016;79(9):096702.
- A-C. Knopf, A. Lomax, Phys. Med. Biol 2013;58(15):R131-60.
- A.C. Kraan, Frontiers in Oncology 2015

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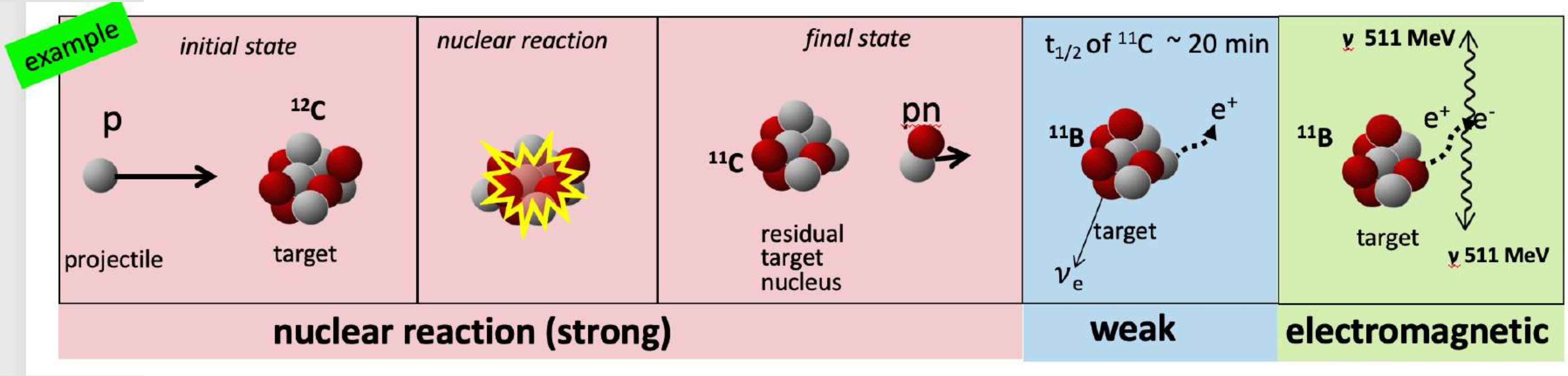
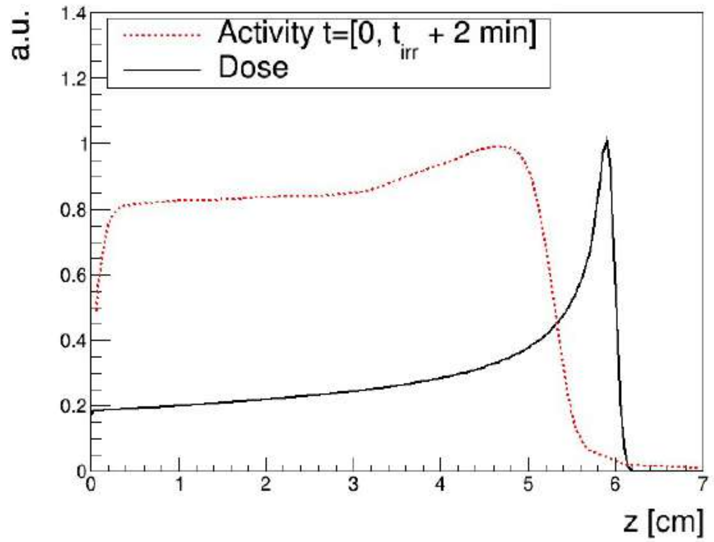


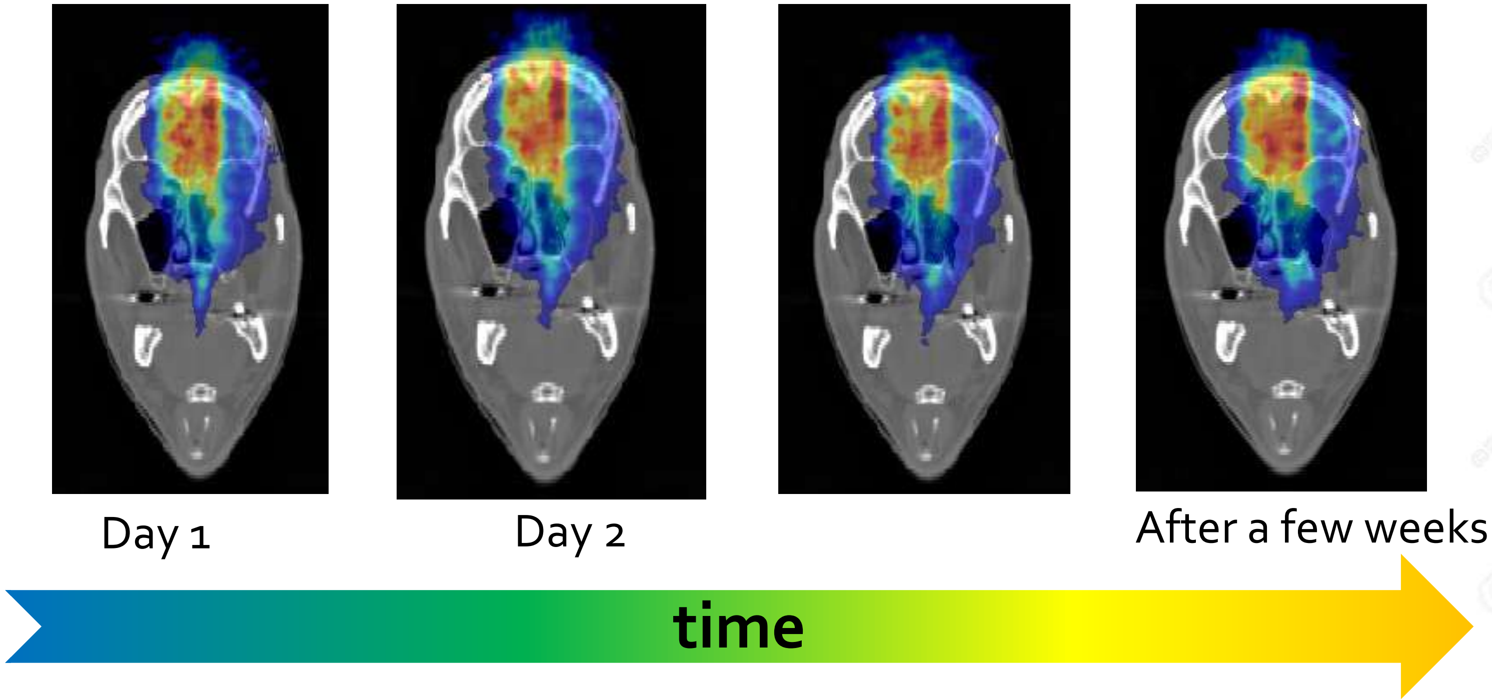
- Among nuclear fragments produced are β^+ emitters Positron Emission Tomography (PET) can be used for in-vivo non-invasive treatment monitoring in proton therapy
  - Indirect relationship between dose and induced PET-activity

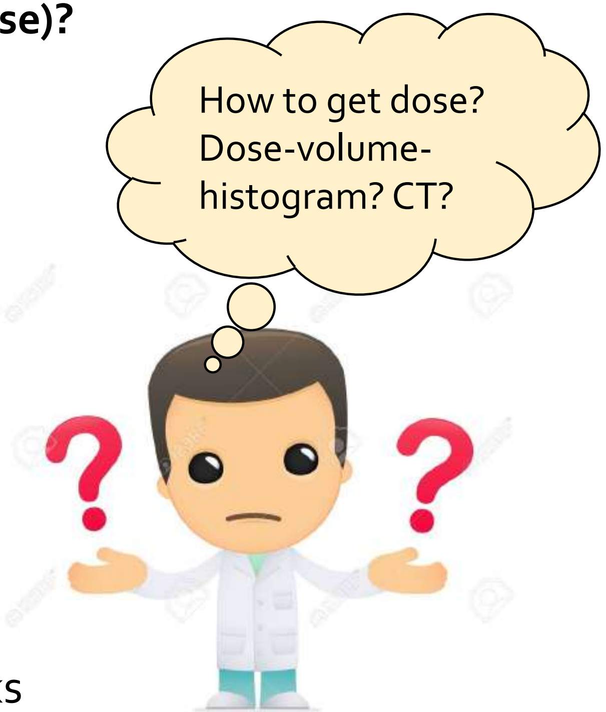


PET treatment monitoring

- K. Parodi, J. C Polf, Review: In vivo range verification in particle therapy, Med Phys 2018 45(11)
- V. Rosso, In-treatment tests for the monitoring of proton and carbon-ion therapy with a large area PET system at CNAO Nuc. Instr.Meth A 824, 228
- P. Dendooven et al, 8923-47Short-lived positron emitters in beam-on PET imaging during proton therapy Phys Med Biol 2015;60(23):

- Much research since 2004…
- Among the problems:
  - Washout of PET signal: most centers had offline PET
  - No straightforward method to translate information from PET into information for clinical personnel
- INSIDE@CNAO: in-beam PET, i.e. data acquisition during and right after treatment
  - Hardly any washout (sensitive to short-lived isotopes)
- **How to translate PET images into clinically relevant information (CT or dose)?**
  - **How to compare these images one with another?**

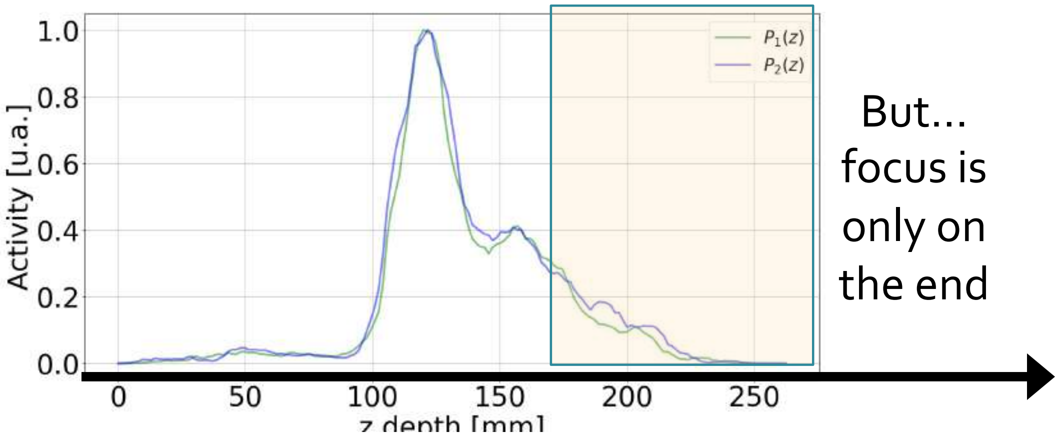




Goal of this study

How to compare images along the treatment?

- Simple subtraction?→generally doesn't work
- Look at end of particle range? (most clinically used methods): Some nice results obtained! But not 3D



But… focus is only on the end

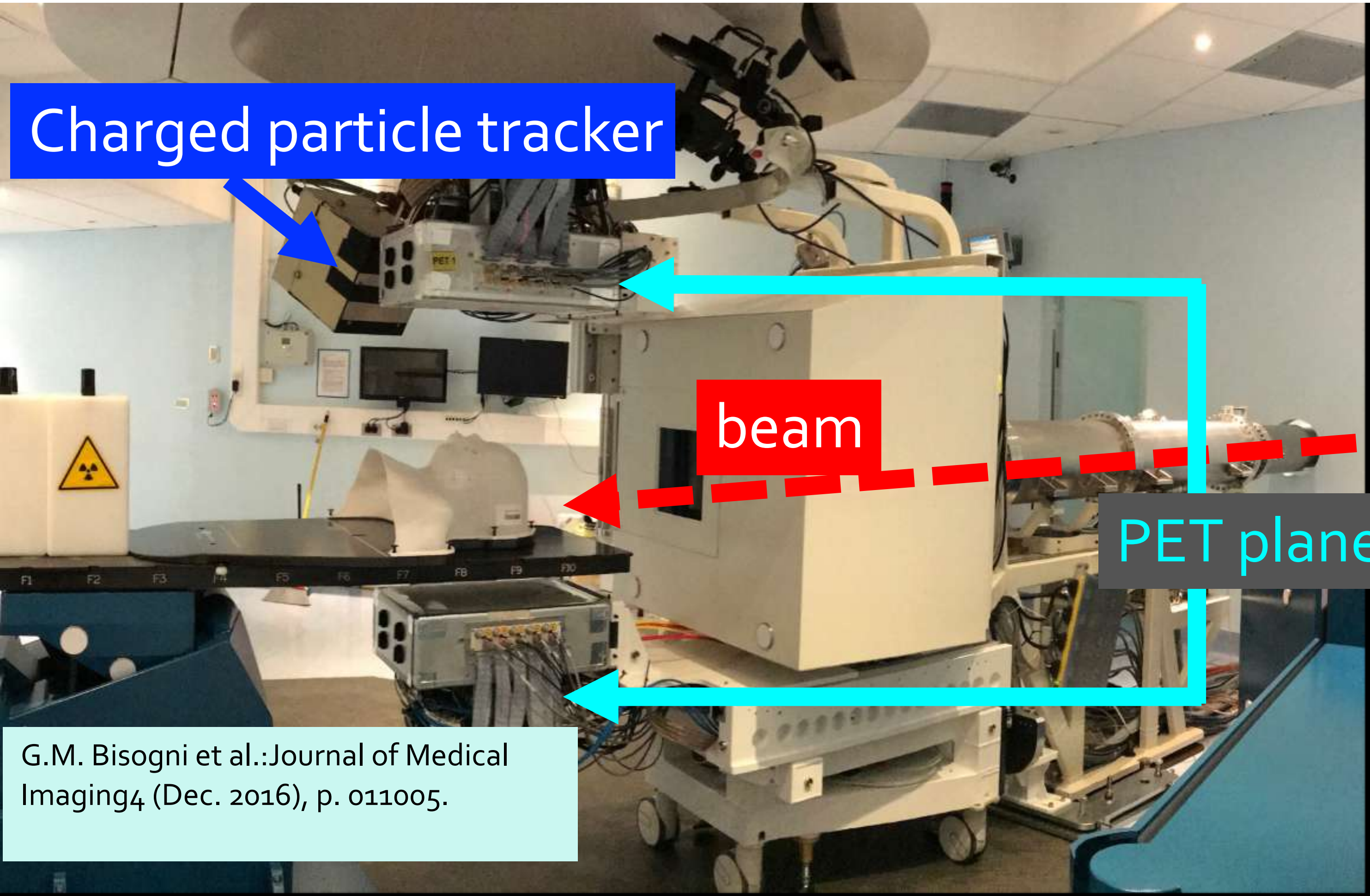
Beam direction

Frey K, et al, Phys. Med.Biol. 59 (2014) 5903–5919.
Knopf A, et. al., Phys. Med. Biol. 53 (2008) 4137–4151.
Ferrero V, et al, IEEE TRPMS 2 (2018) 588–593.
Fiorina E ,et al, Frontiers in Physics 8 (2021) 578388.
Moglioni et al, accepted in Frontiers of Oncology, June 2022.

In this work test a new approach

- Voxel-based: use the 3-D distribution to localize difference
  → step closer to CT and dose reconstruction?
- Use the gamma-analysis method, commonly used for dose comparisons

Methods and Materials: INSIDE



INSIDE detector :

- In-beam
- Designed in 2010-2013
- Constructed 2014-2016
- Installed at CNAO (National Centre of Oncological Hadrontherapy) since 2016
  - Clinical trial since 2018 (slide16)
  - Operated during beam delivery and up to about 30 seconds after

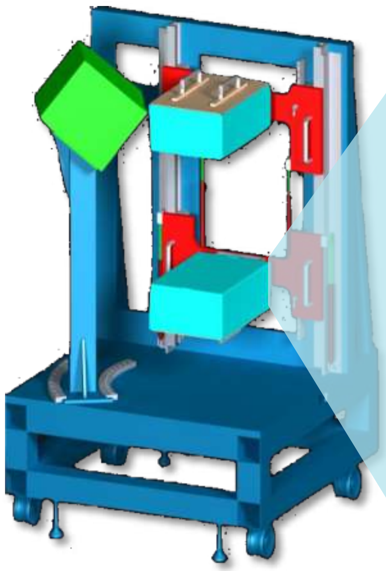
Innovative Solution for
Dosimetry **in** Hadronthreapy

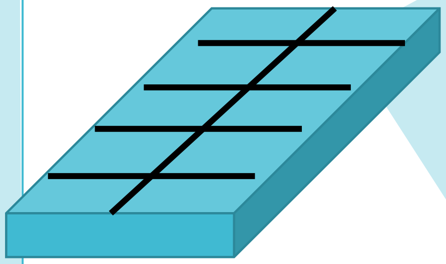
CNAO

M&M: INSIDE PET detector

Main features

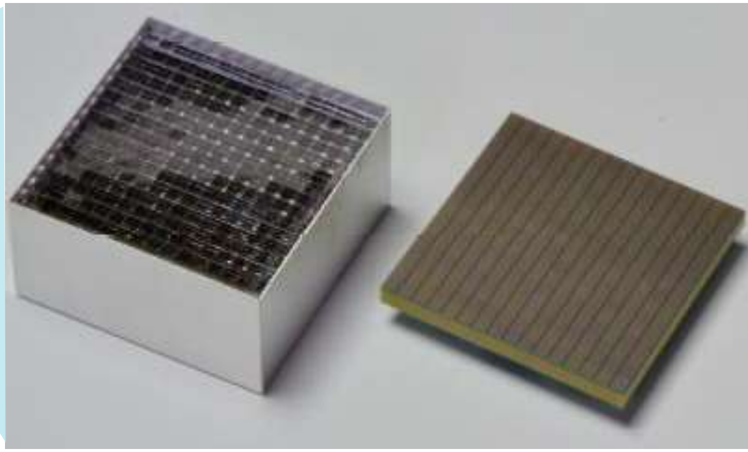
- coincidence window = 2 ns
- CTR = 450 ps (sigma)
- Energy resolution ~ 13 MeV
- Image reconstruction method: Maximum Likelihood Expectation Method





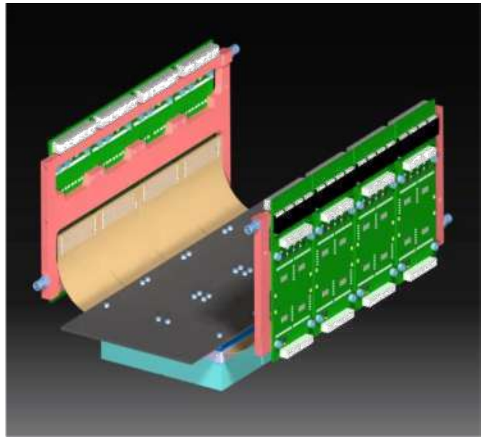
10x 25 x 5 cm^3
Distance from the isocenter=25 cm

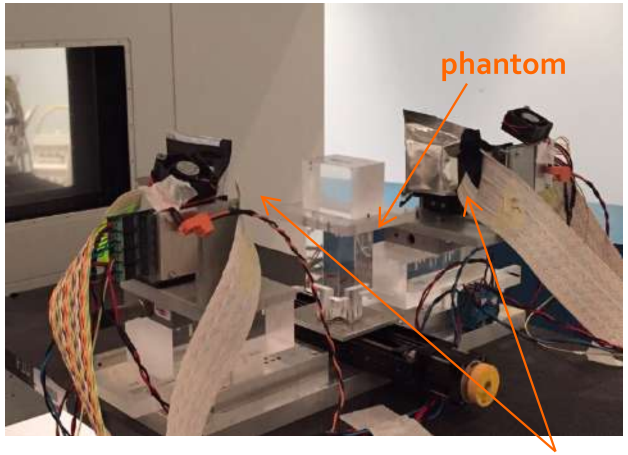
Courtesy of A. Del Guerra. Krakow 2015



256 LFS pixel crystals (3x3x20mm^3) coupled one to one to MPPCs (Multi Pixel Photon Counters, SiPMs).

Solid model of the PET head

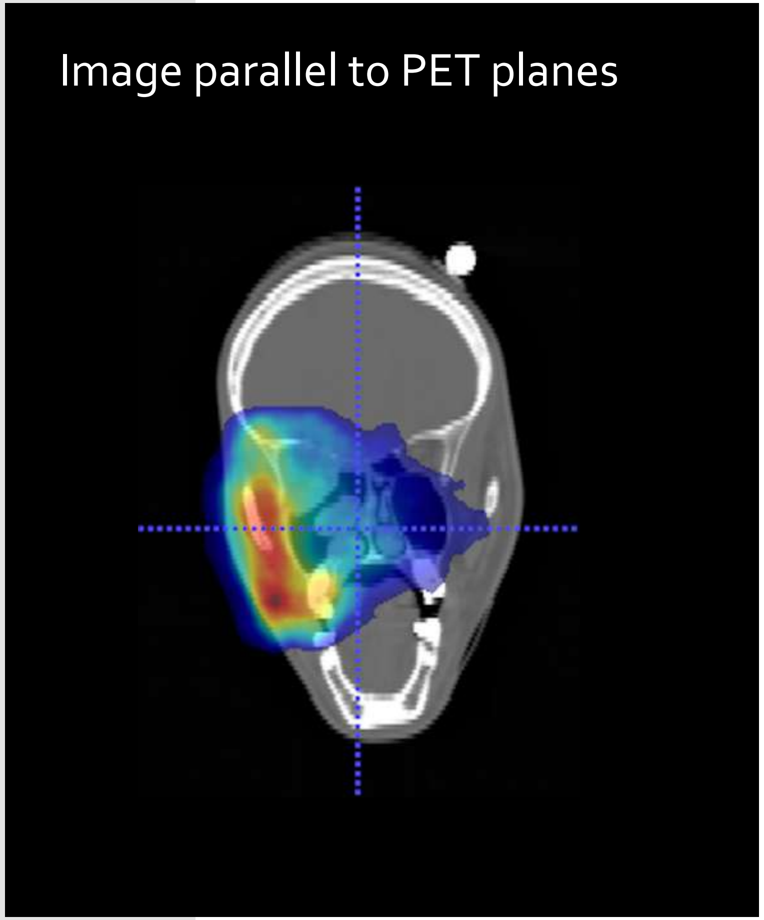


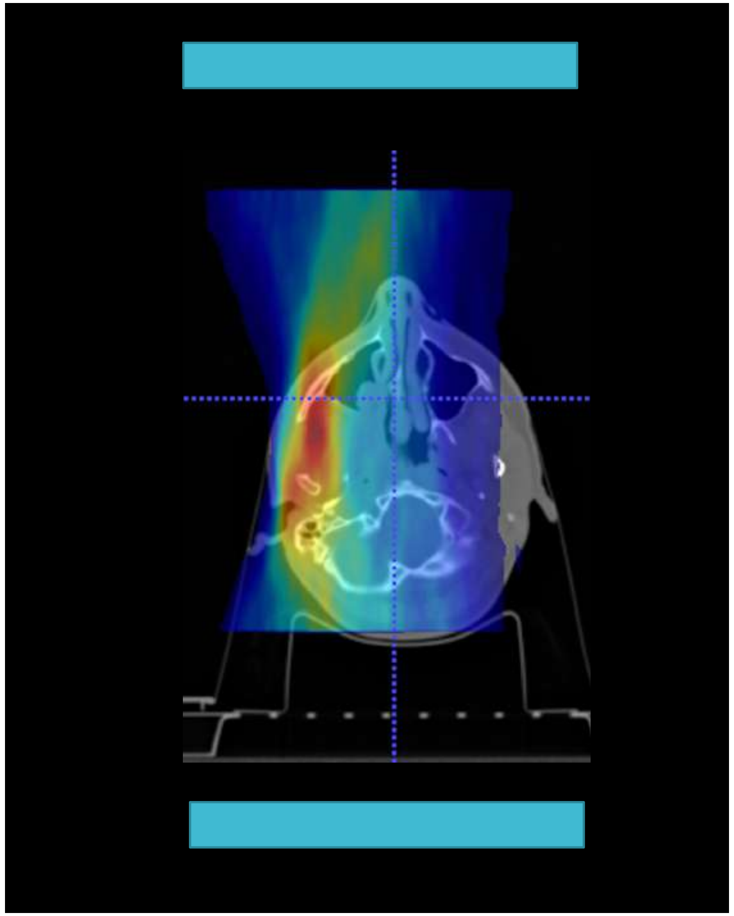


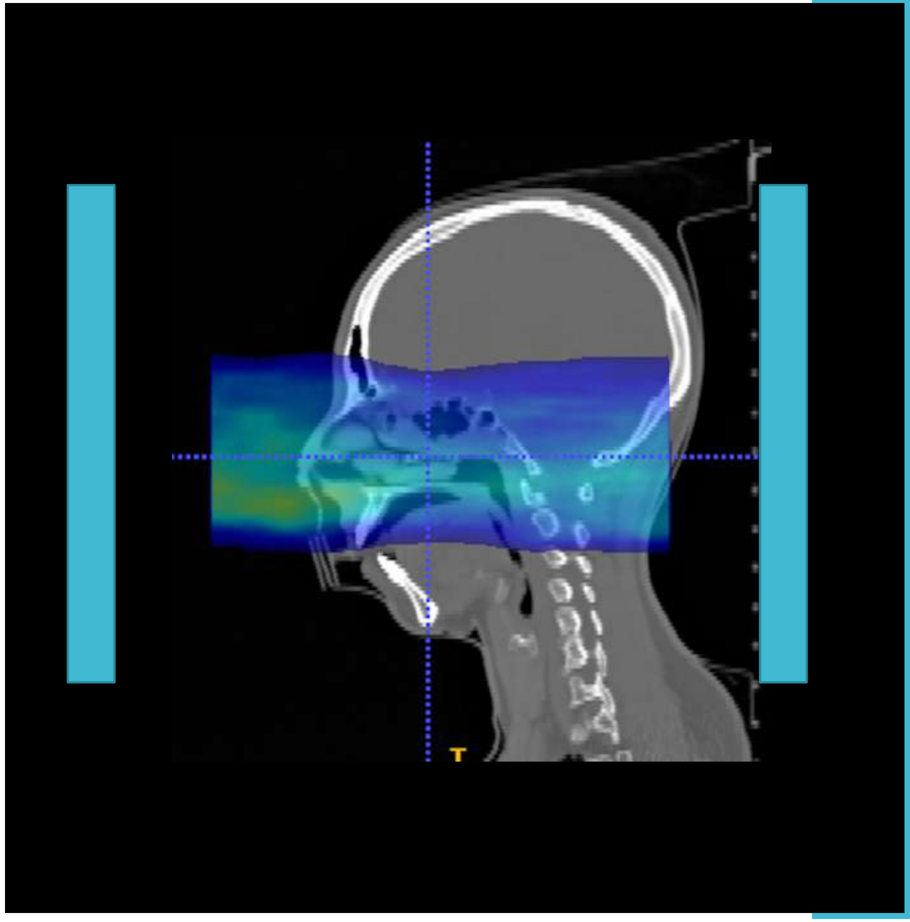
G.M. Bisogni et al.:Journal of Medical Imaging4 (Dec. 2016), p. 011005.

M&M: INSIDE PET detector

Example image from data



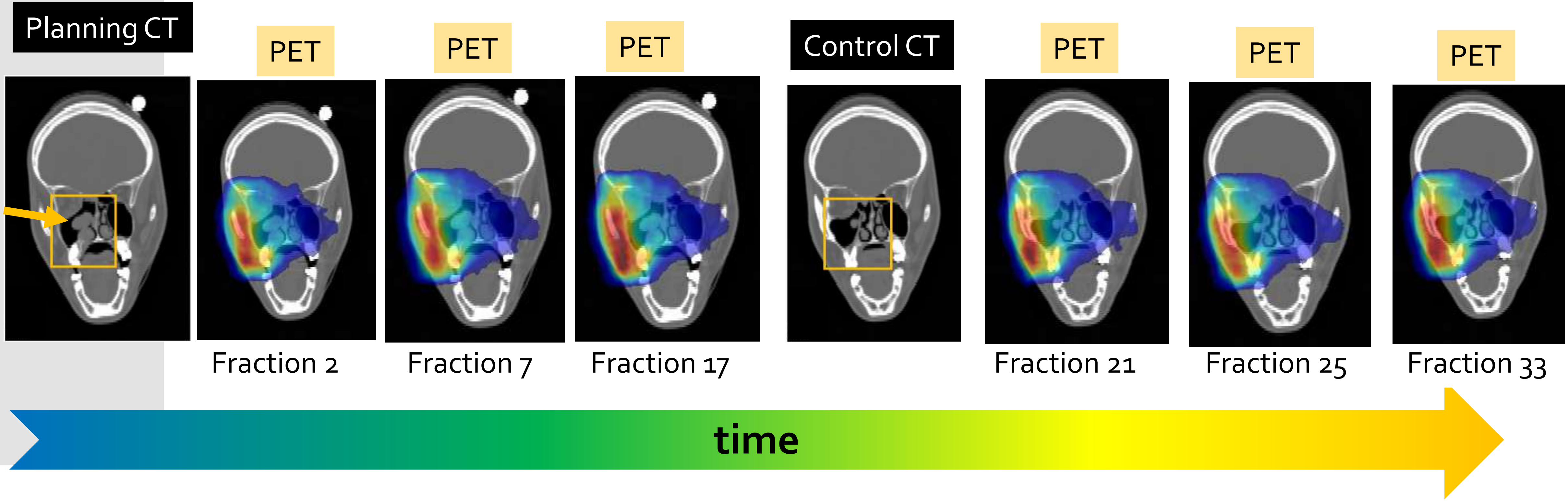




Patients monitored with INSIDE

- Since 2018: clinical trial at CNAO: ClinicalTrials.gov ID: NCT03662373
- 10 proton therapy patients, 10 carbon therapy patients

Example of patient
- Adenoid Cystic Carcinoma (glandular tissues) treated with protons
- patient had a small change after about 3 weeks (from control CT)



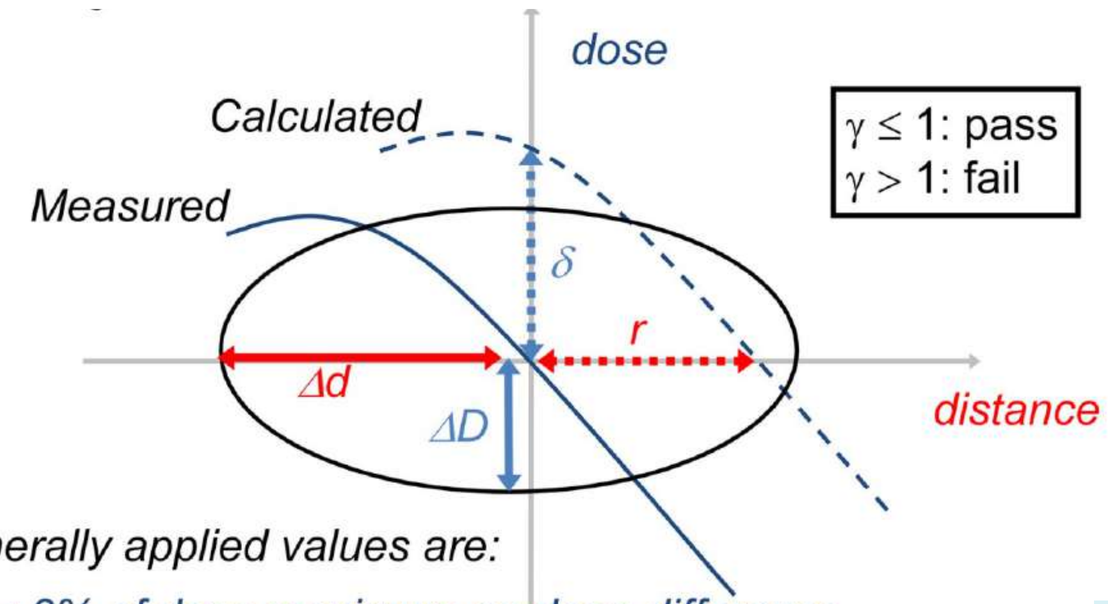
How to compare these images...?

Methods and Materials: γ-evaluation analysis

The γ-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)

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

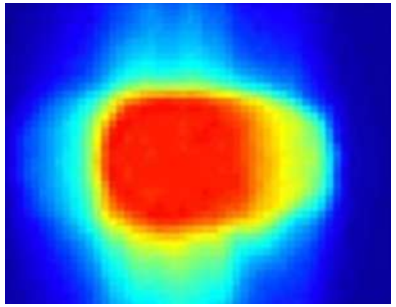
Methods and Materials: γ-evaluation analysis

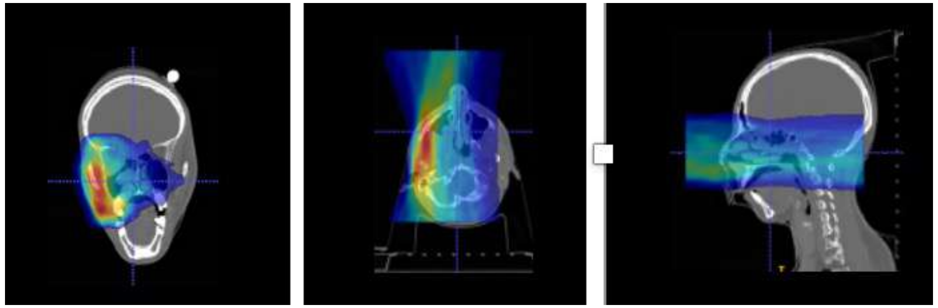
Widely used for dose comparisons

Application of the γ-analysis to PET is challenging!

Problems:
- No existing recommendations for tolerances and thresholds…
- Hardly used
    - 1 example found, Knopf, IROBP 2011, 70, 297
- PET distributions are not homogeneous
- In-beam PET images:
    - Contain artefacts
    - Noisy

Approach:
- Empirical
- Start with Monte Carlo simulations to understand tolerances…
- Then test on data

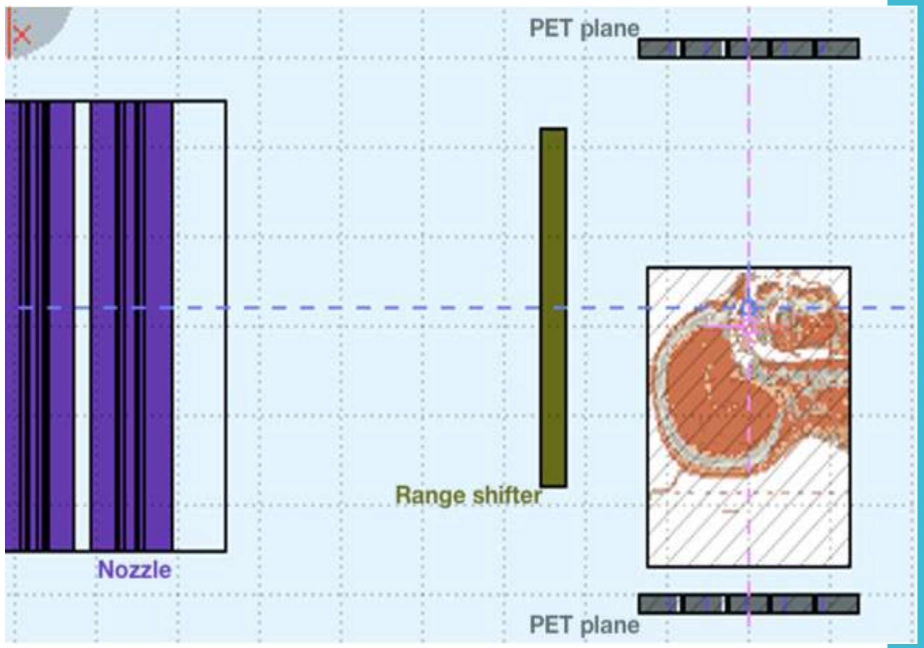




Methods and Materials: simulations

FLUKA simulation code used

- Input:
  - Patient CT
  - Treatment plan
  - Geometry: INSIDE at CNAO
- Simulation
- Image reconstruction with Maximum Likelyhood Estimation Method
- Output:
  - PET image



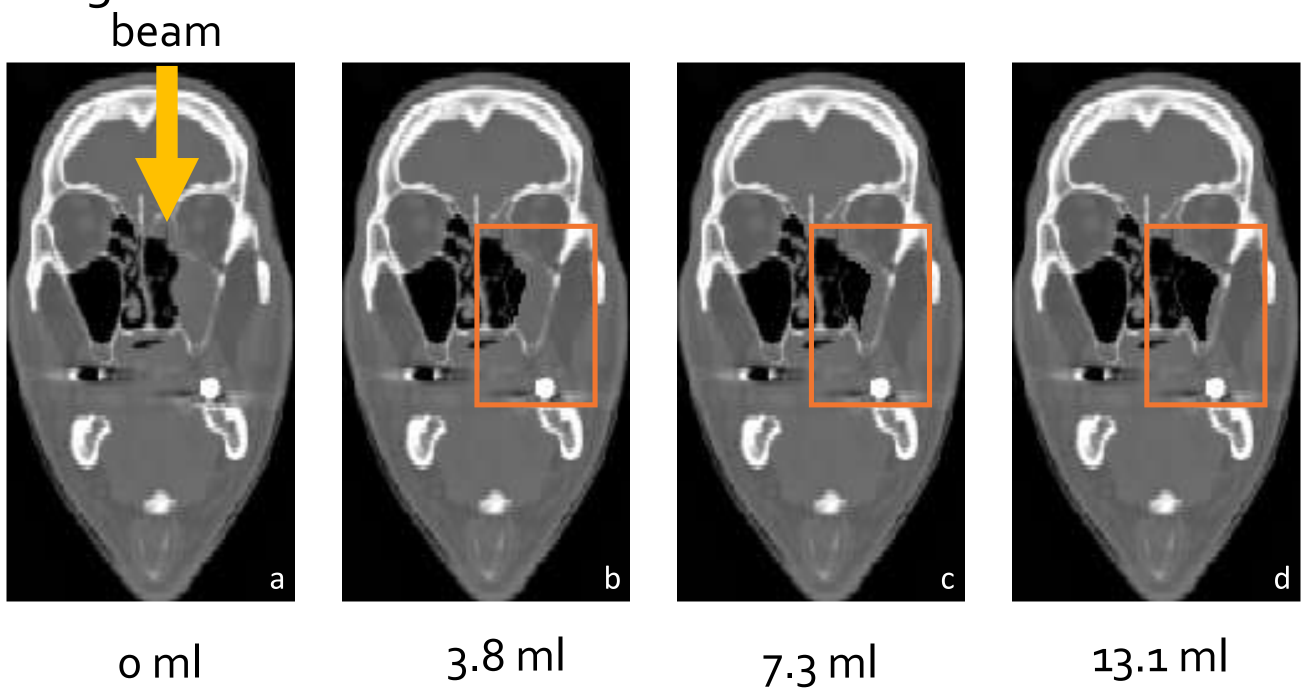
Pennazio F, et al Carbon ions beam therapy monitoring with the inside in-beam pet. Phys Med Biol (2018 Jul 17)

Methods and Materials: simulations

Create samples with anatomical changes

- ✓ Create a reference PET image without modifications
- ✓ Create a series of artificially modified CT scans that include anatomical changes, mimicking emptying of sinonasal cavity along the course of treatment
- ✓ Generate the corresponding PET images with FLUKA

mod. CT j	ΔV[ml]	ΔV[%]
0	0	0
1	1.9	15
2	3.8	29
3	5.7	44
4	7.3	56
5	10.2	78
6	13.1	100



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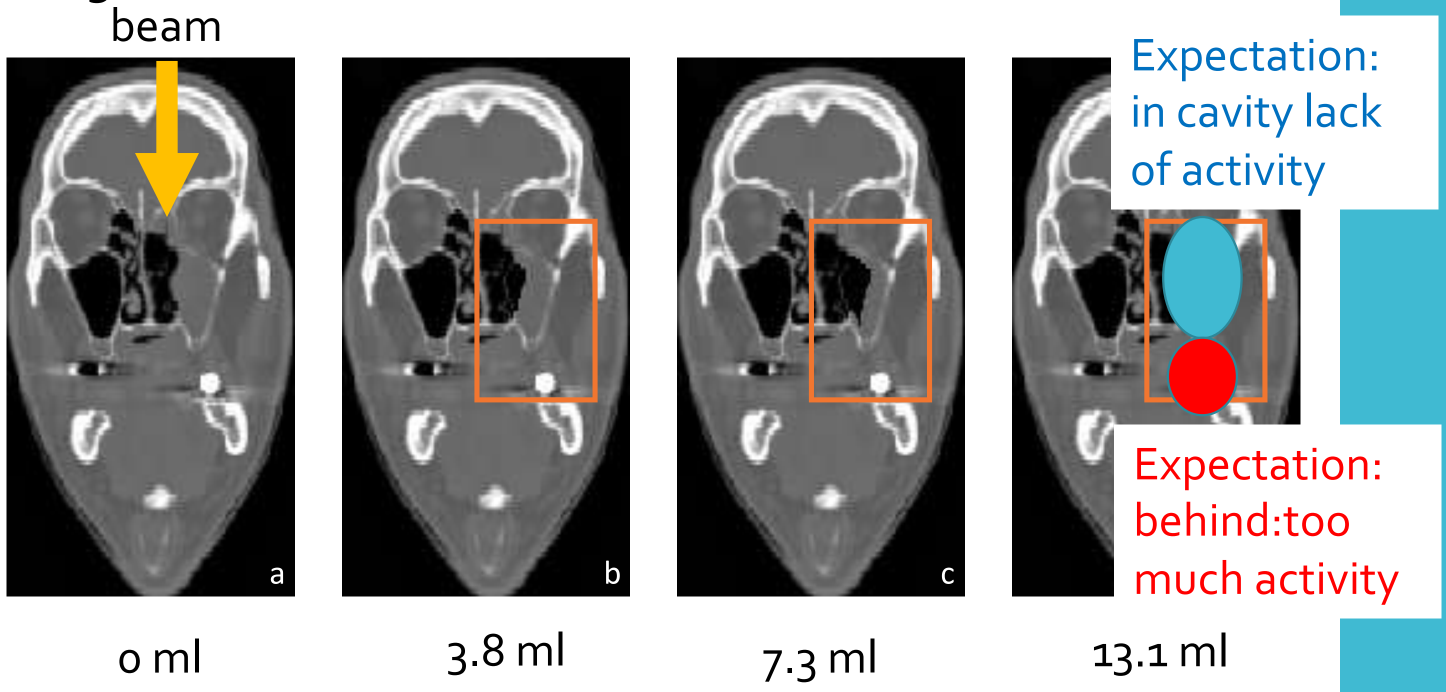
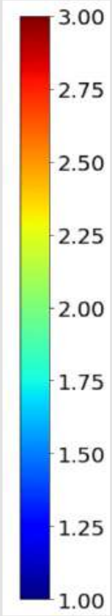


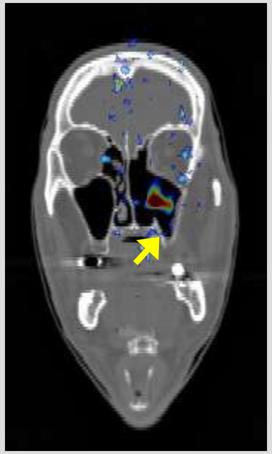
Results: choice of threshold and tolerances

- To determine threshold and tolerances, compare 0 ml with **13 ml**
- Plot the voxels with gamma >1 (disagreement)

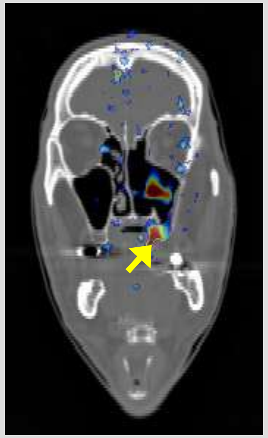


Threshold

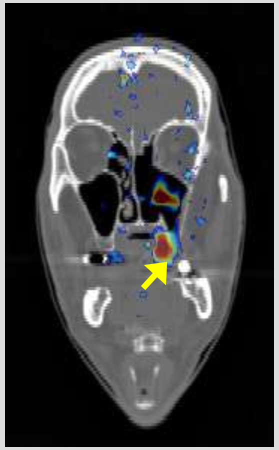
DTA=3mm
DD=3%
TH=10%
Overshoot not visible + falsely identified voxels



DTA=4mm
DD=4%
TH=5%
Overshoot not visible



DTA=4 mm
DD=4%
TH=2%
Overshoot + cavity visible

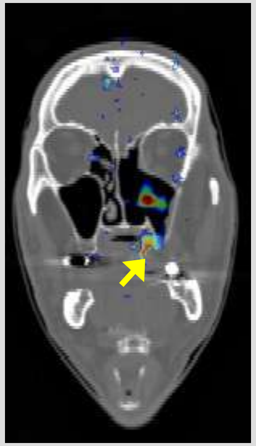


DTA=4 mm
DD=4%
TH=1%
Overshoot + cavity visible

Tolerances

DTA=2mm
DD=2%
TH=2%
Many falsely identified voxels

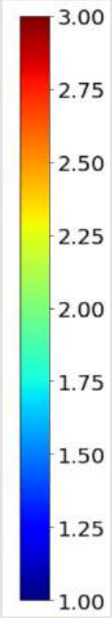
DTA=4 mm
DD=4%
TH=2%
Overshoot + cavity visible



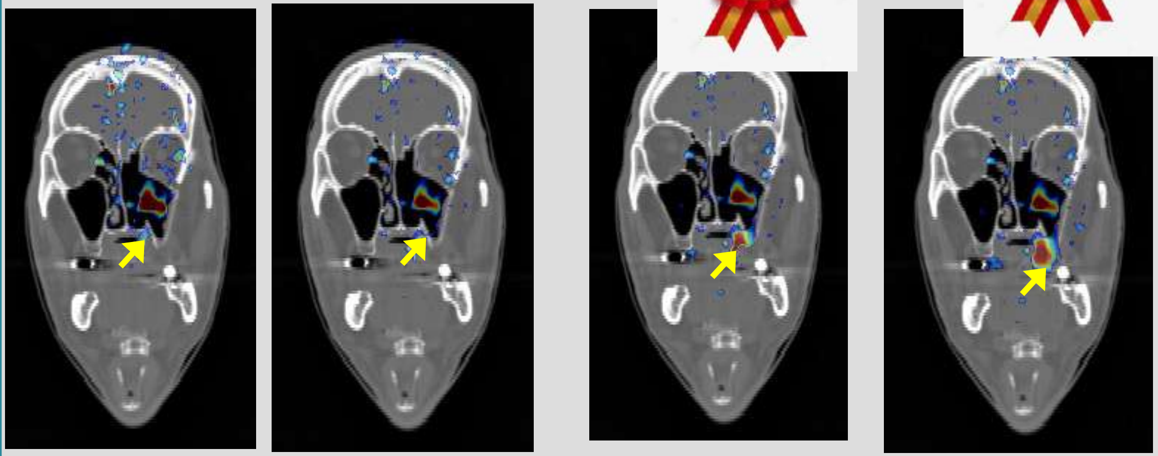
DTA=5 mm
DD=5%
TH=2%
Overshoot just visible

Results: choice of threshold and tolerances

- To determine threshold and tolerances, compare o ml with **13 ml**
- Plot the voxels with gamma >1 (disagreement)

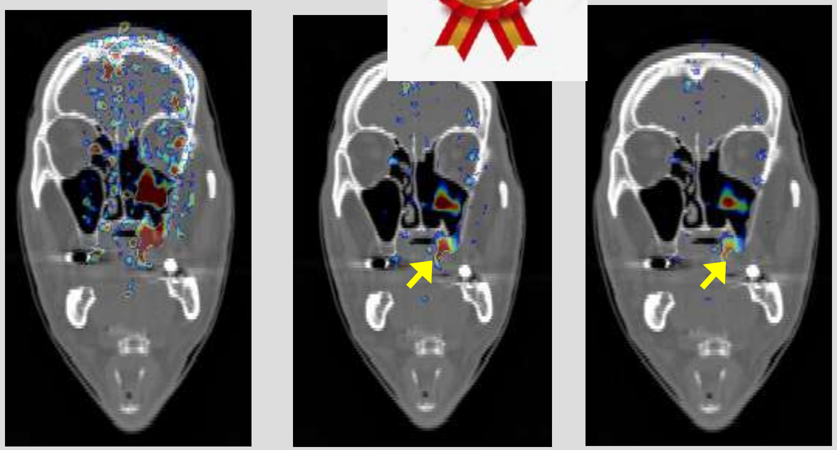


Threshold



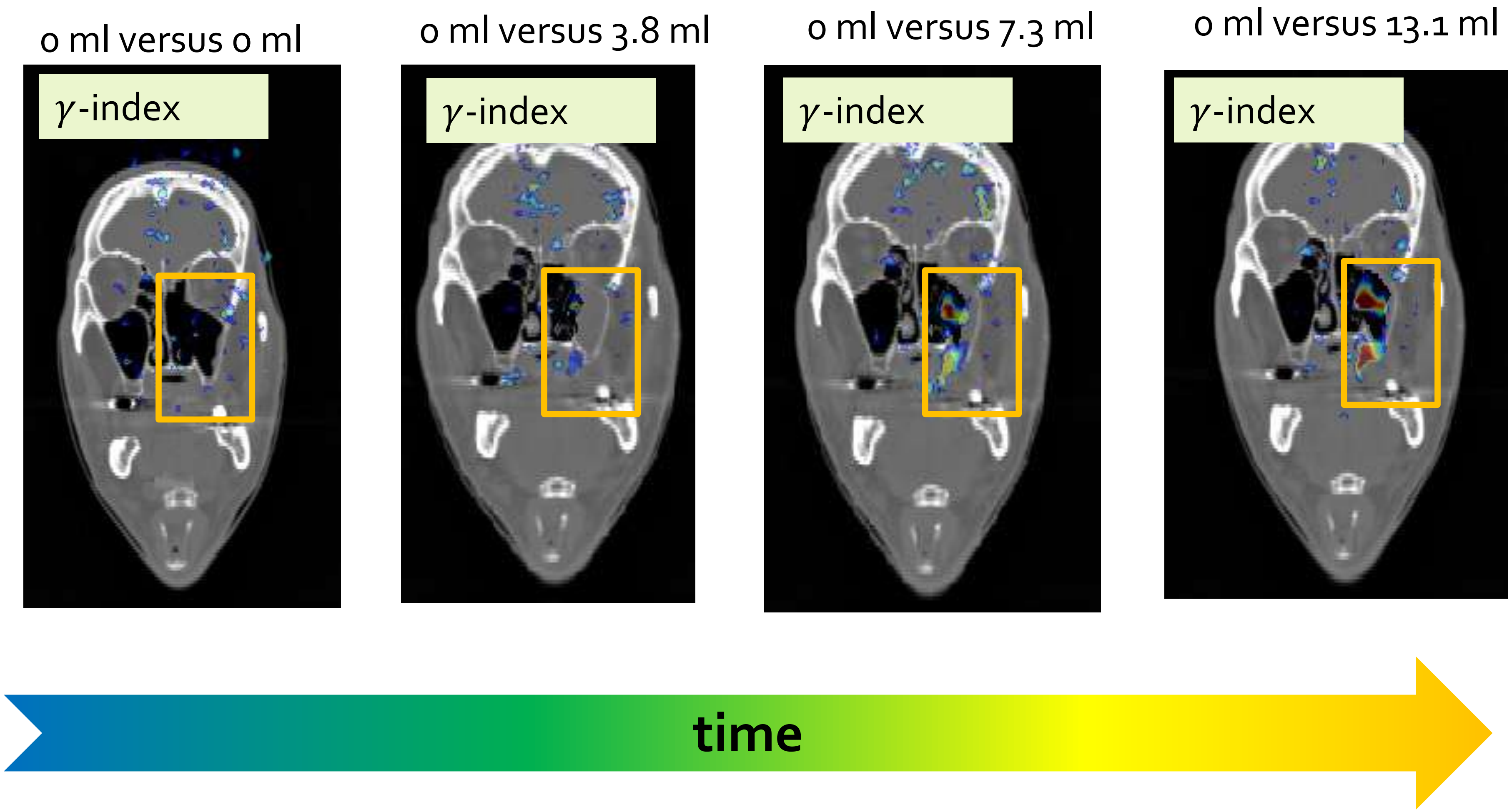
DTA=3mm DD=3% **TH=10%** Overshoot not visible + falsely identified voxels	DTA=4mm DD=4% **TH=5%** Overshoot not visible	DTA=4 mm DD=4% **TH=2%** Overshoot + cavity visible	DTA=4 mm DD=4% **TH=1%** Overshoot + cavity visible
✗	✗	✓	✓

Tolerances



DTA=2mm **DD=2%** TH=2% Many falsely identified voxels	**DTA=4 mm** **DD=4%** TH=2% Overshoot + cavity visible	**DTA=5 mm** **DD=5%** TH=2% Overshoot just visible
✗	✓	✗

Results: trend over time (simulations)



DTA=4 mm
DD=4%
TH=2%

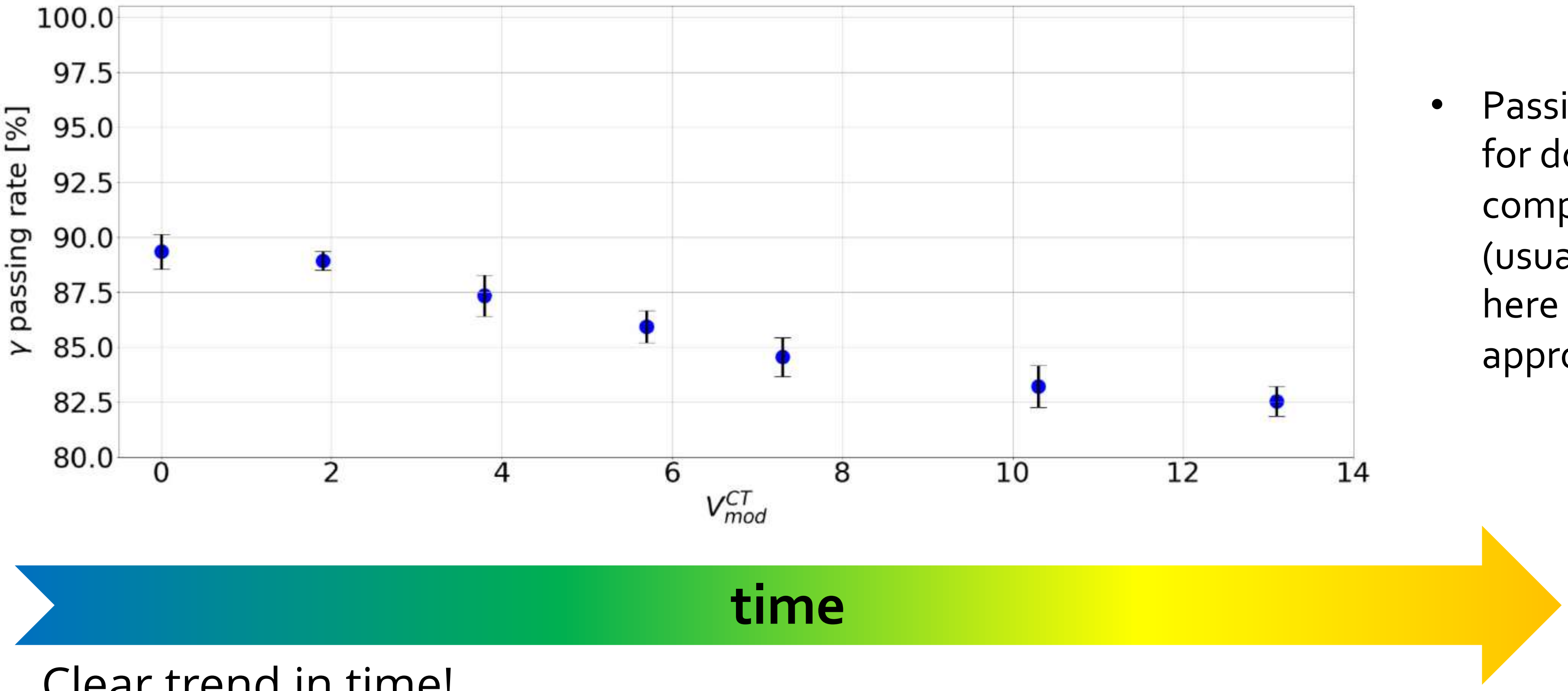
- Only the problematic regions highlighted now!!
- Gamma analysis works despite ugly activity distribution, artifacts, etc
- Could bring us a step closer to CT and dose reconstruction

Results: passing rate (simulations)

The gamma passing rate:

$$Passing\ rate = \frac{Nr\ of\ voxels\ that\ pass}{Total\ number\ of\ voxels}$$

- Decreasing trend
- Absolute value of passing rate is not 100 %from the start (one random seed versus another) → statistical errors
- Error determined by performing multiple simulations with different random seeds

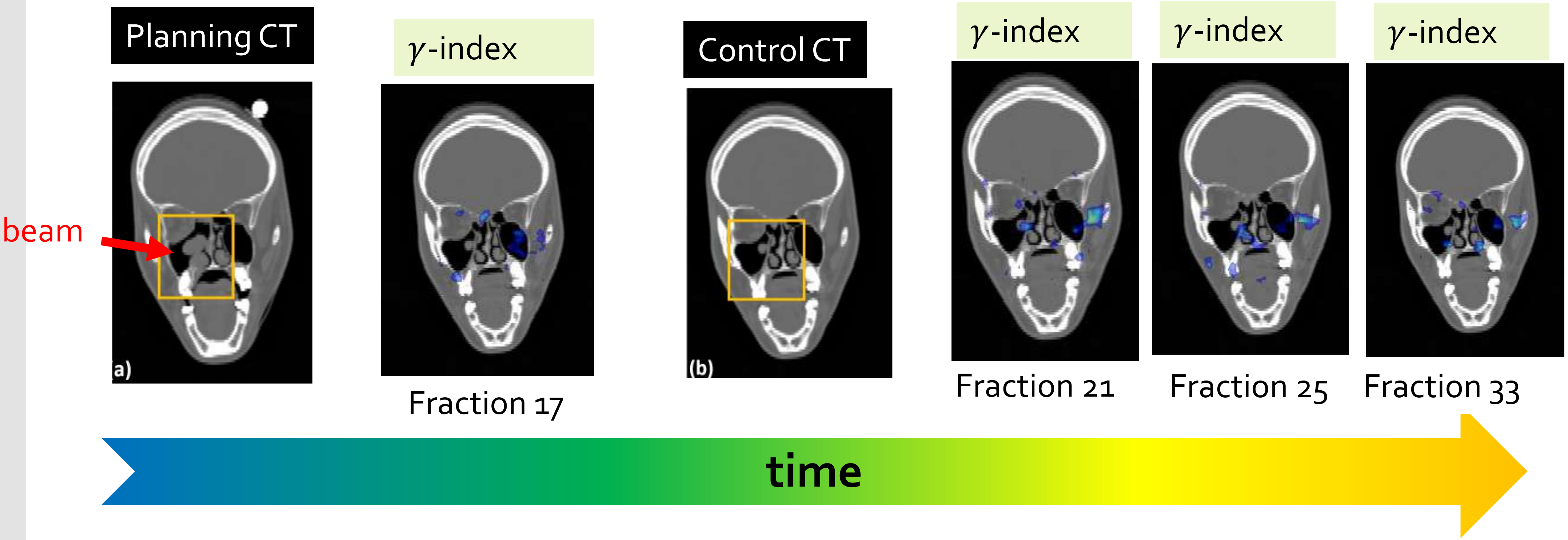


- Passing criteria for dose comparisons (usually 90%) here not appropriate

Clear trend in time!

Results: ACC patient

- **Patient**: Adenoid Cystic Carcinoma treated with protons
- It is known that the patient had a small change after about 3 weeks (from control CT)
- But no new plan was made, change was estimated to not have significant dose impact
- First monitored fractions were used as 'reference'



- Beam overshoot visible in later fractions (in agreement with CT)

Conclusion

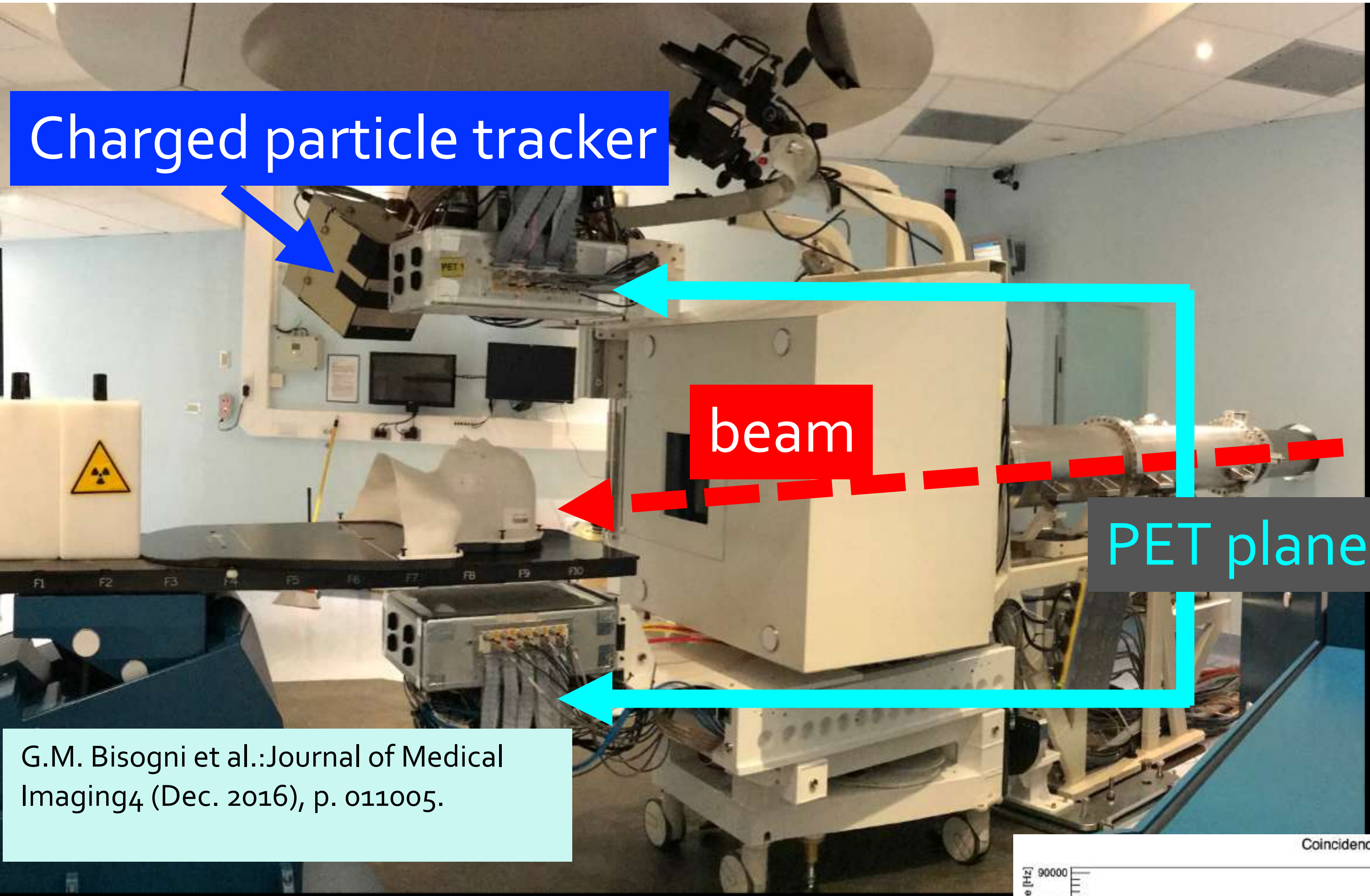
Simulations:

- Gamma-analysis can be applied to in-beam PET images to identify regions with morphological changes
- Tolerances and threshold should be chosen probably somewhat larger than dose comparisons
- For in-beam PET images, absolute value of gamma passing rate is not really a good metric to assess whether changes have taken place.
- But tendency over many treatment fractions can be used

Data

- Preliminary results showed that the changes can be identified
- Trends visible in distributions and in gamma passing rate
- Challenging: the patient had only very small changes…
- Gamma-analysis can be used alone, or even better, in combination with 'end-of-range' verification methods

Methods and Materials: INSIDE



G.M. Bisogni et al.:Journal of Medical Imaging4 (Dec. 2016), p. 011005.

INSIDE detector :

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  - Close to nozzle
  - Operated during beam delivery and up to about 30 seconds after
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