

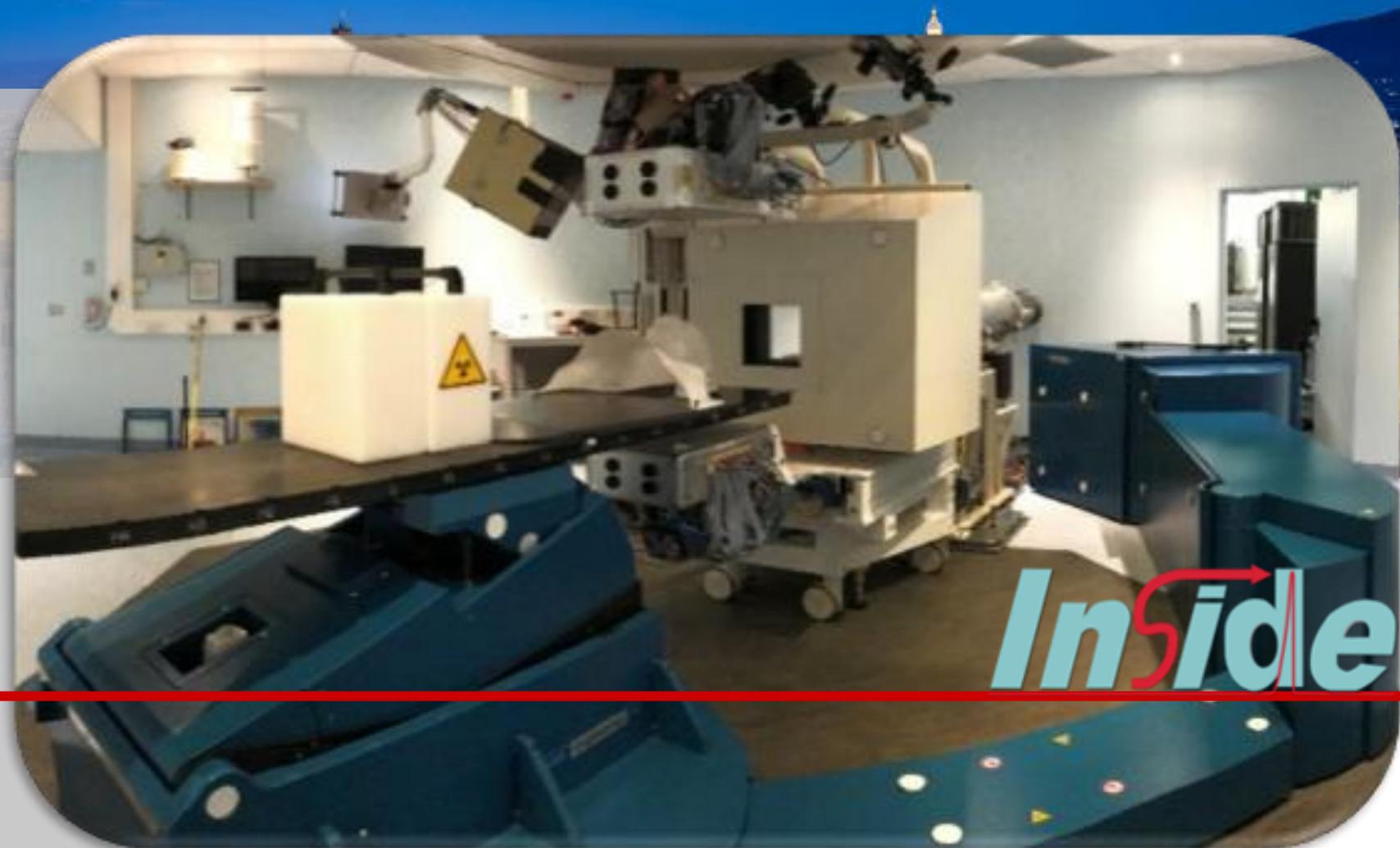
ion 2025 Imaging workshop

6th Ion Imaging Workshop
October 20-21, 2025 Florence, Italy

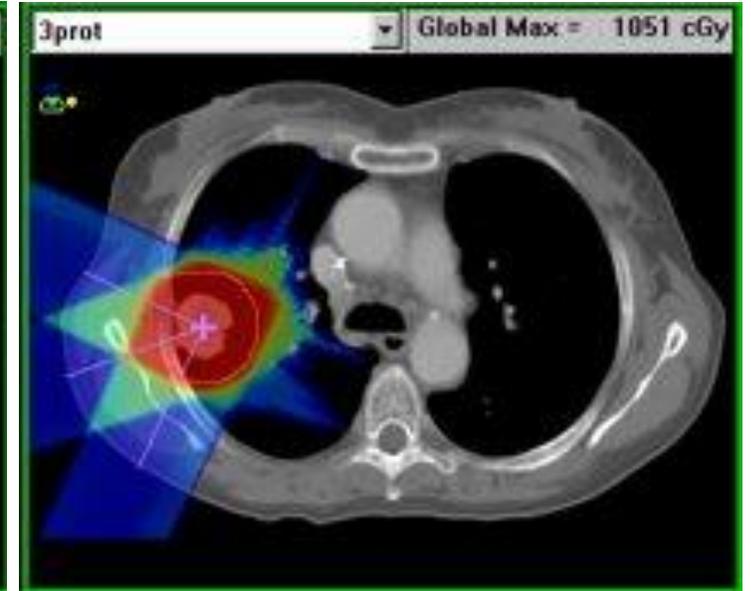
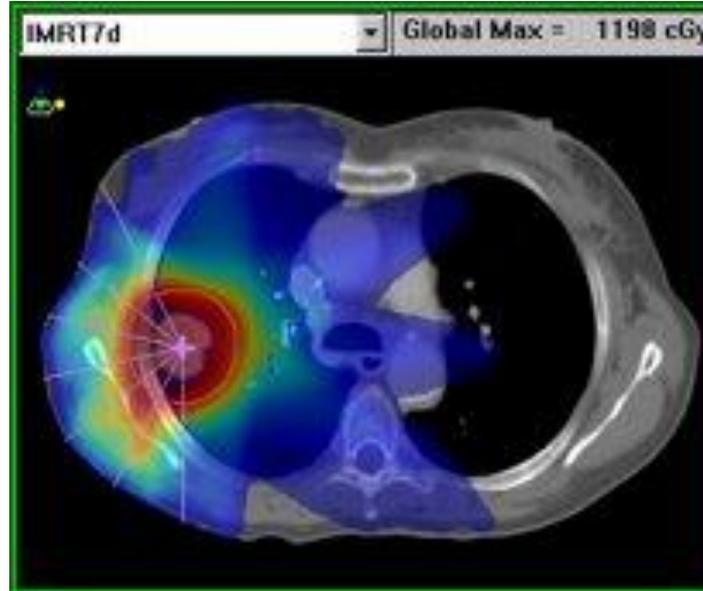
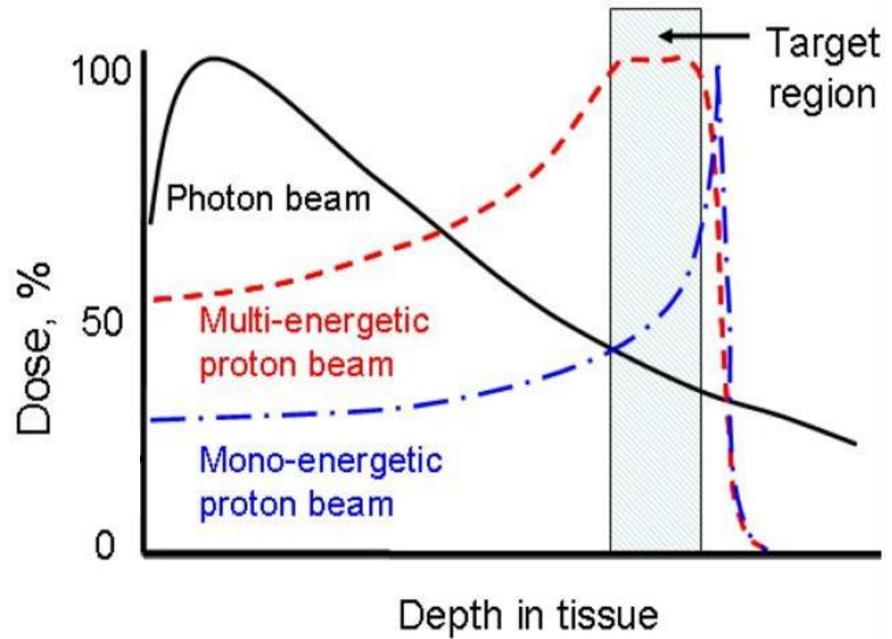
Results update of the INSIDE clinical trial for head-and-neck cancer: in-vivo treatment verification by means of in-beam PET

F. Pennazio, M. G. Bisogni, A. M. Camarda, P. Cerello, M. Ciocca, E. Data, V. Ferrero, E. Fiorina, K. Haddad, A. Kraan, M. Moglioni, M. Morrocchi, S. Ranjbar, A. Retico, I. B. Rivas Ortiz, V. Rosso, G. Sportelli, G. Traini, B. Vischioni, V. Vitolo

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Particle Therapy

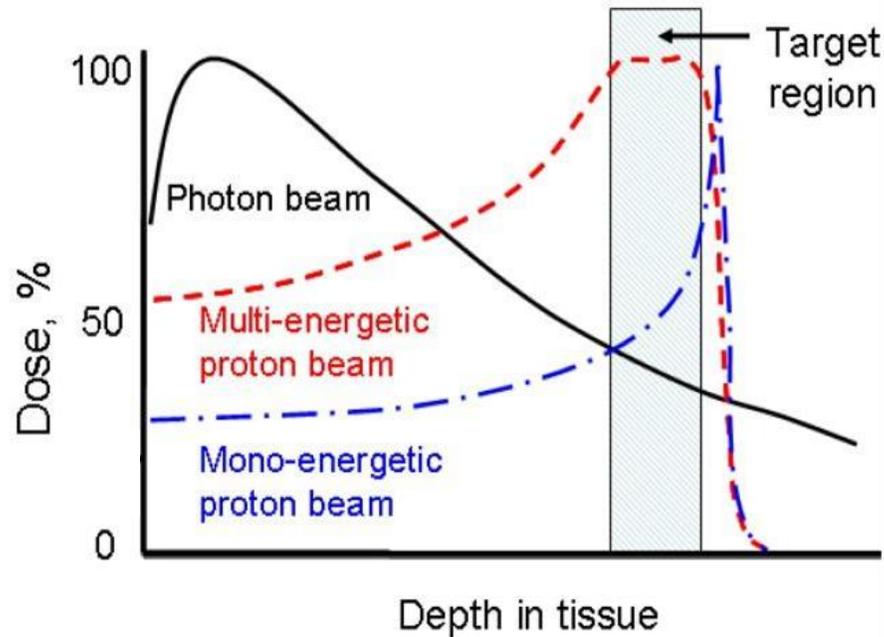


favourable depth dose deposition (Bragg peak)
+
enhanced radiobiological effectiveness for heavier ions
=
reduced integral dose
better sparing of organs-at-risk



reduced toxicity
lower secondary malignancy risk
increased tumour local control

Particle range uncertainty



Range uncertainty estimation for robust treatment plans
2.5-3% + 1-3 mm

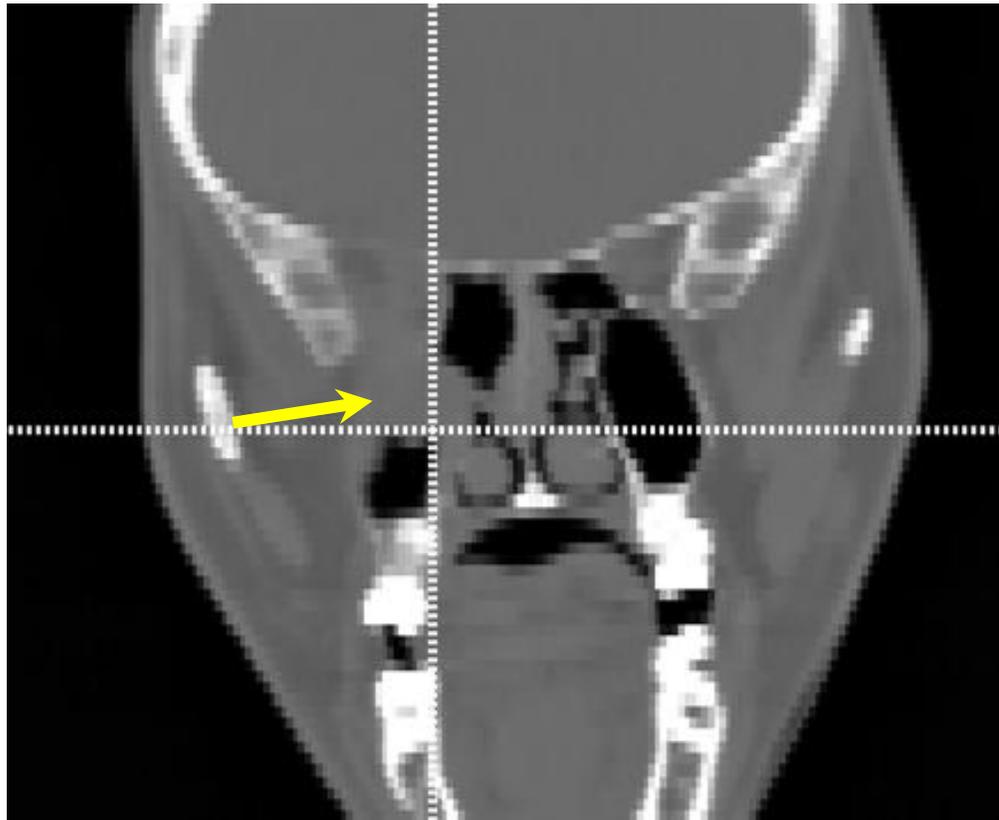
Source of range uncertainty in the patient	Range uncertainty without Monte Carlo	Range uncertainty with Monte Carlo
Independent of dose calculation:		
Measurement uncertainty in water for commissioning	± 0.3 mm	± 0.3 mm
Compensator design	± 0.2 mm	± 0.2 mm
Beam reproducibility	± 0.2 mm	± 0.2 mm
Patient setup	± 0.7 mm	± 0.7 mm
Dose calculation:		
Biology (always positive) [^]	+ ~0.8% ^g	+ ~0.8% ^g
CT imaging and calibration	± 0.5% ^b	± 0.5% ^b
CT conversion to tissue (excluding I-values)	± 0.5% ^a	± 0.2% ^d
CT grid size	± 0.3%	± 0.3%
Mean excitation energy (I-values) in tissues	± 1.5% ^e	± 1.5% ^e
Range degradation; complex inhomogeneities	- 0.7% ^e	± 0.1 %
Range degradation; local lateral inhomogeneities *	± 2.5% ^f	± 0.1 %
Total (excluding *, ^)	2.7% + 1.2 mm	2.4% + 1.2 mm
Total (excluding ^)	4.6% + 1.2 mm	2.4% + 1.2 mm

Paganetti, Phys Med Biol. 2012

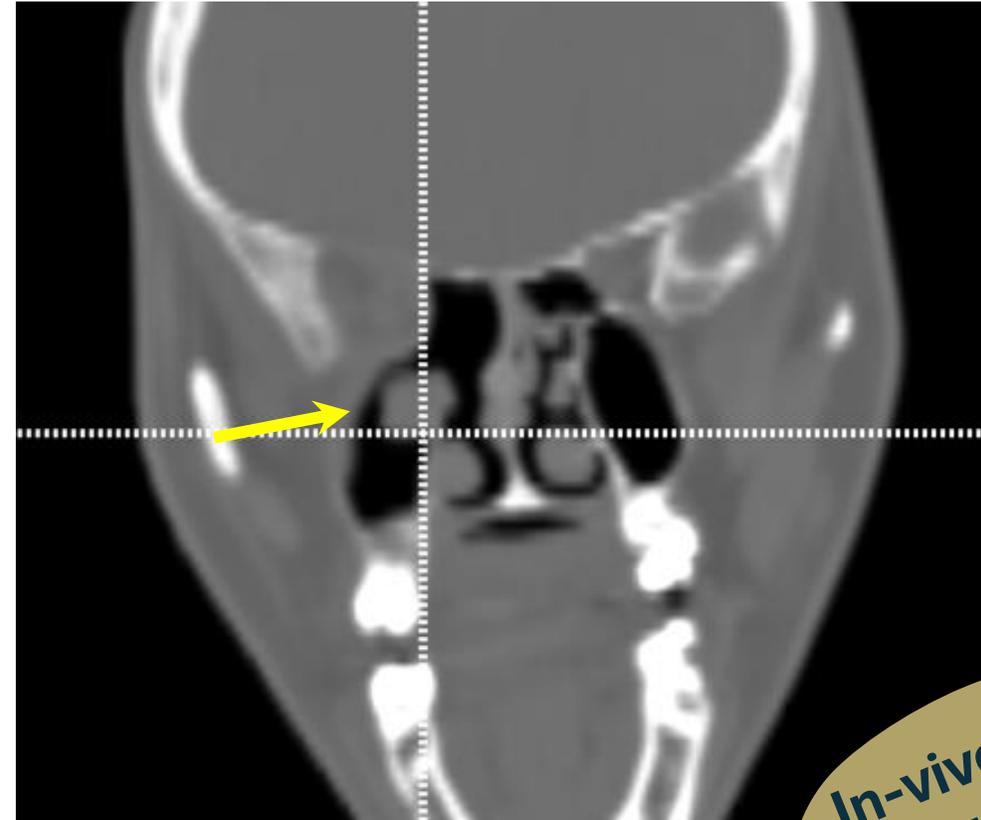
Particle range uncertainty

Interfractional morphological changes!

Planning CT



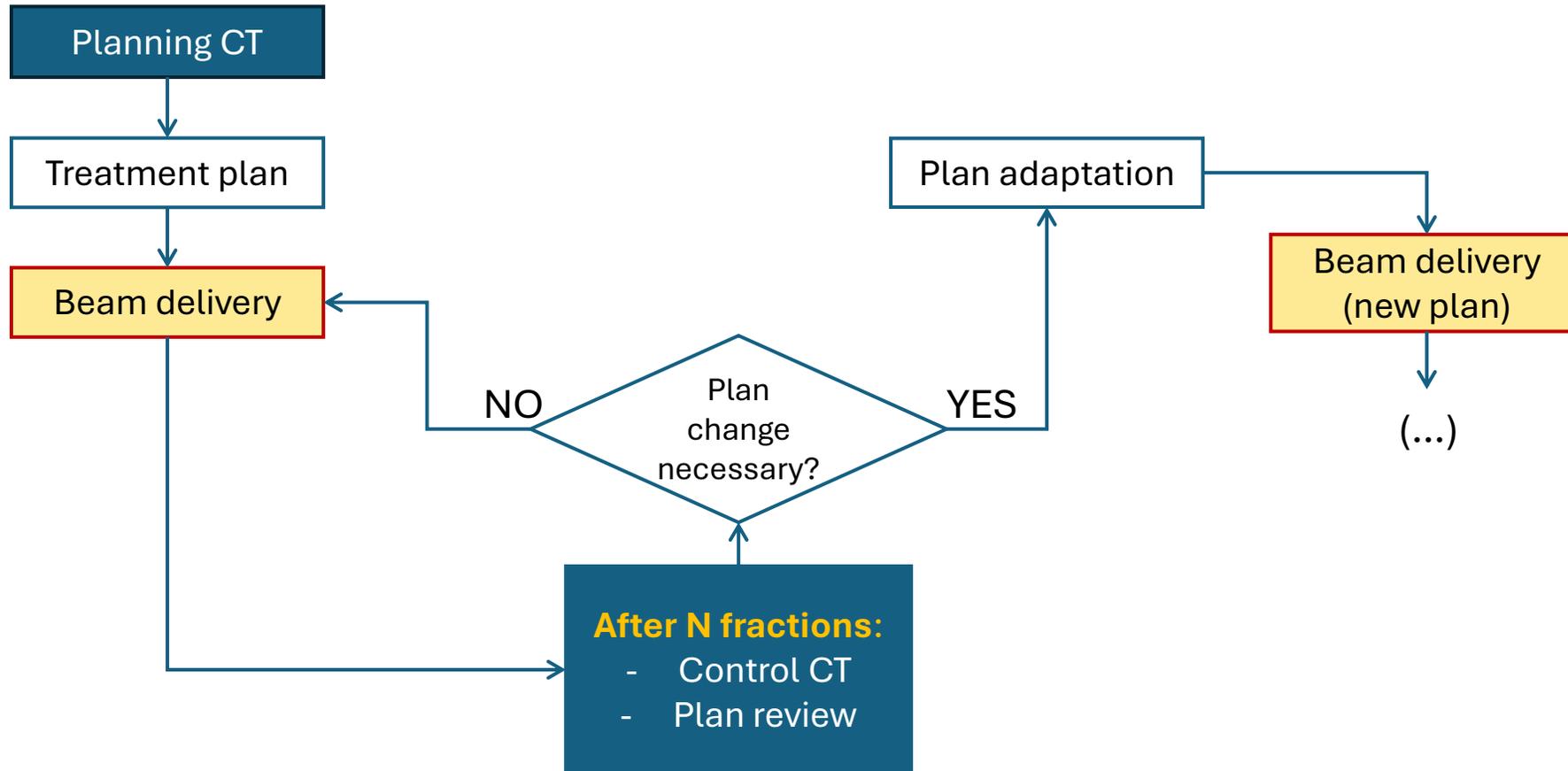
Control CT (21 fraction)



Patient affected by ACC (Adenoid Cystic Carcinoma), treated with protons

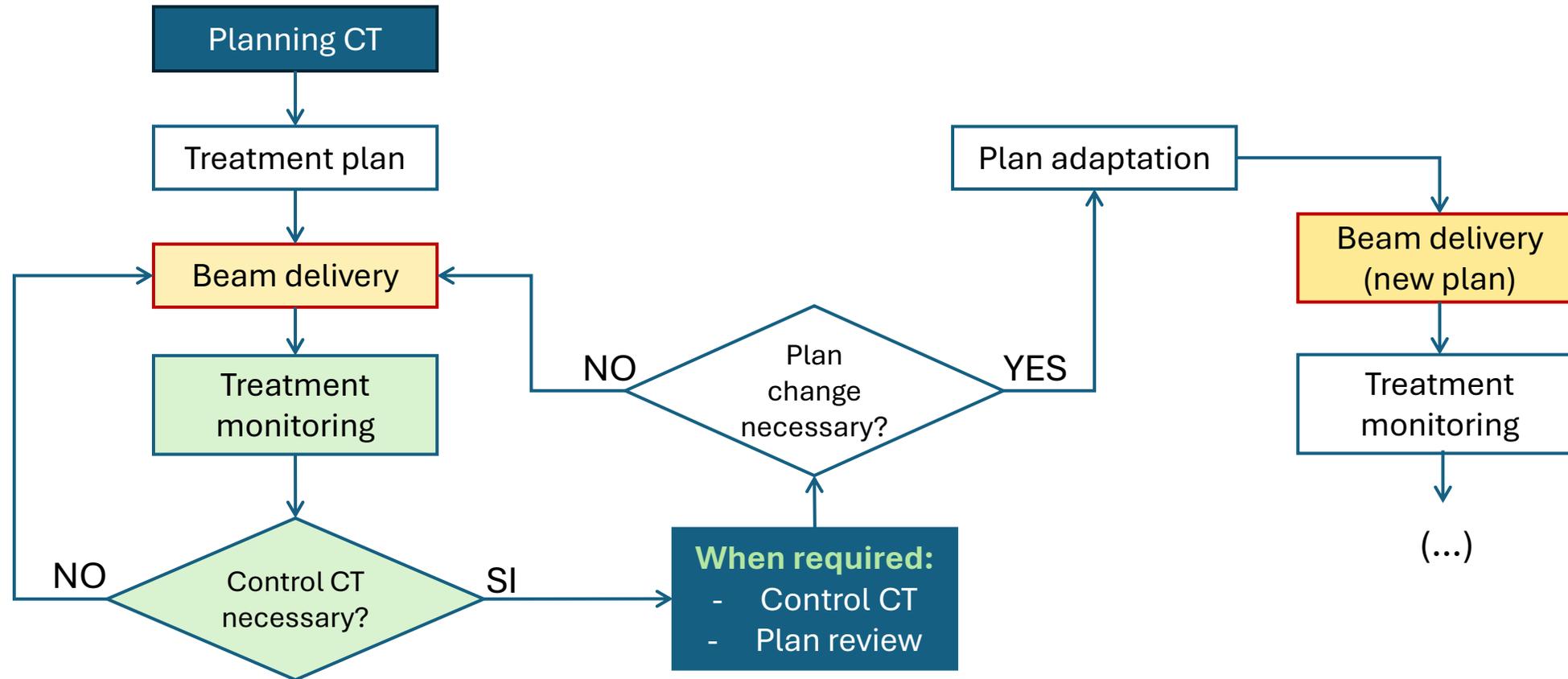
In-vivo range verification!

Interfractional morphological changes!

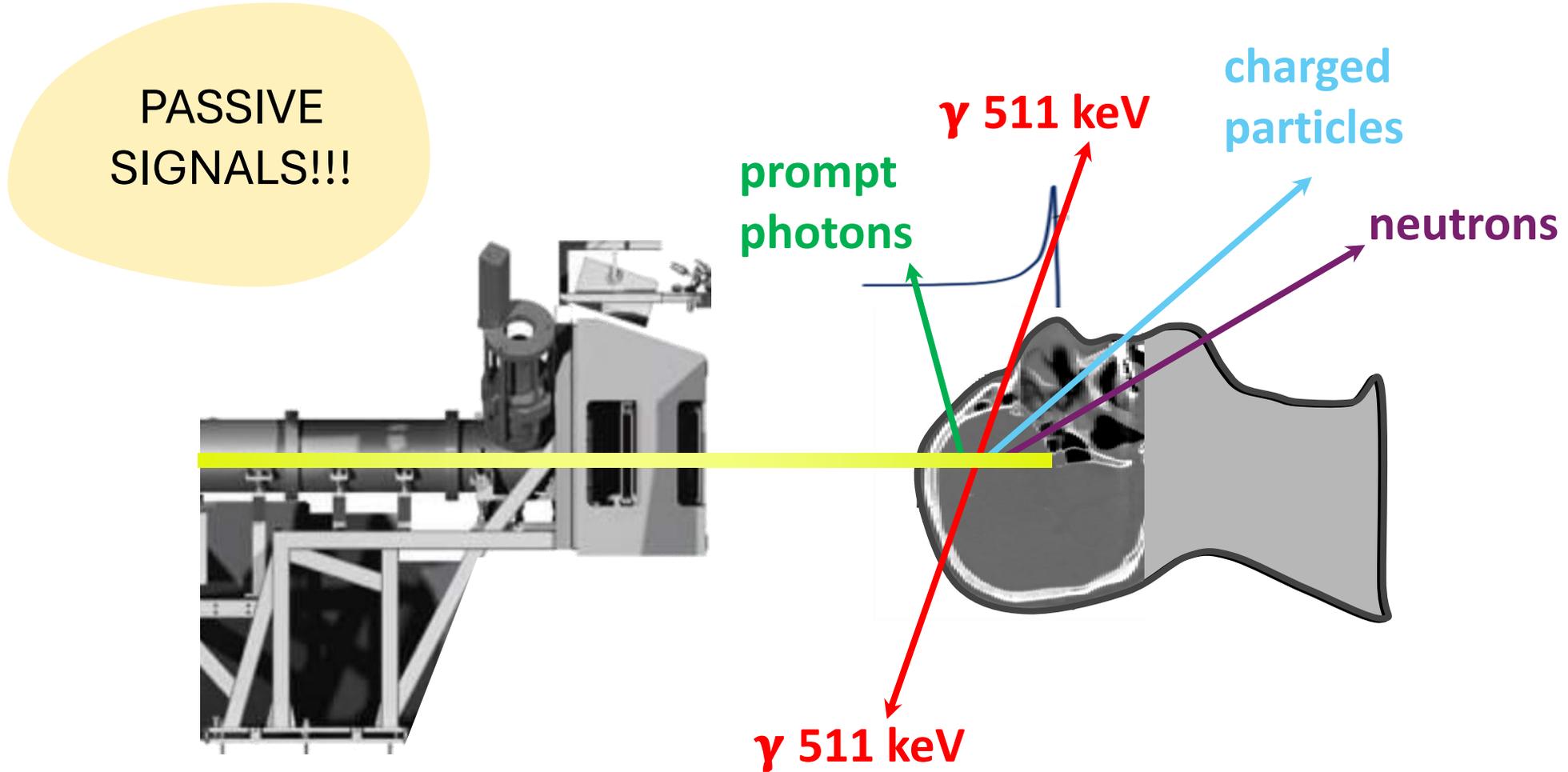


Adaptive therapy

Interfractional morphological changes!

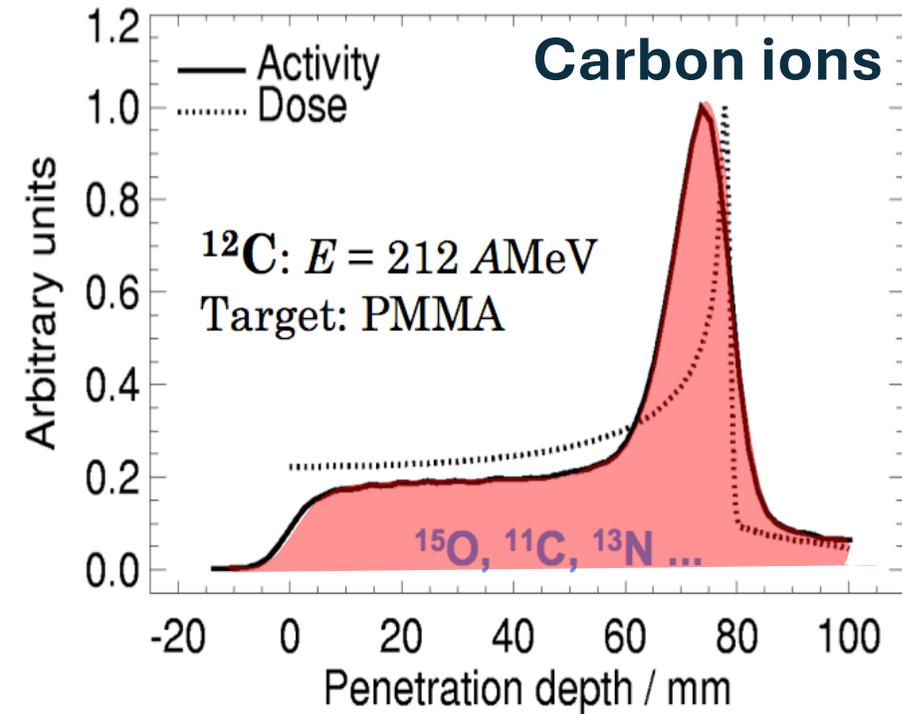
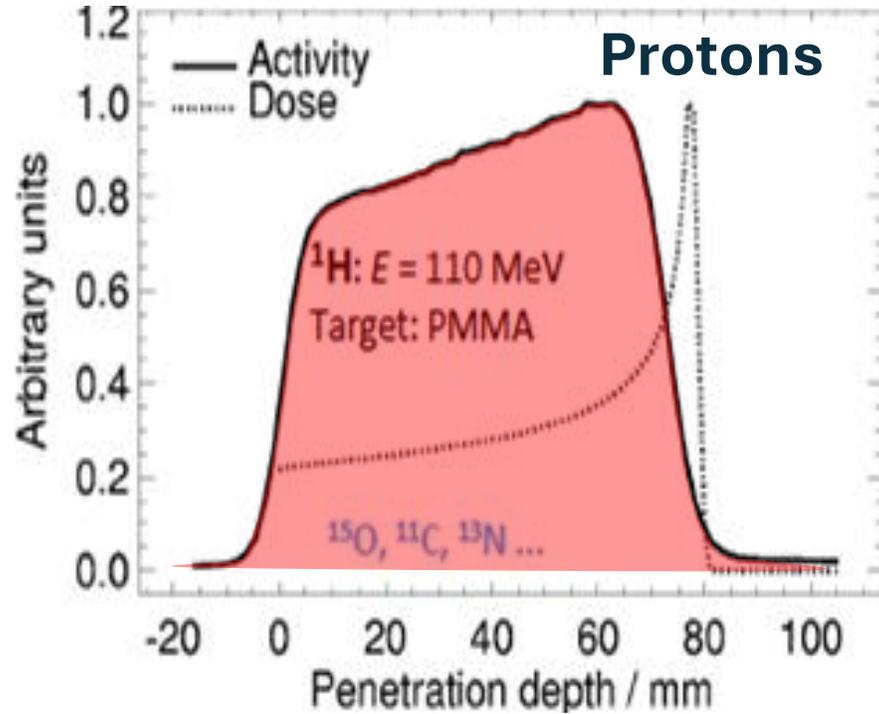


In-vivo range monitoring

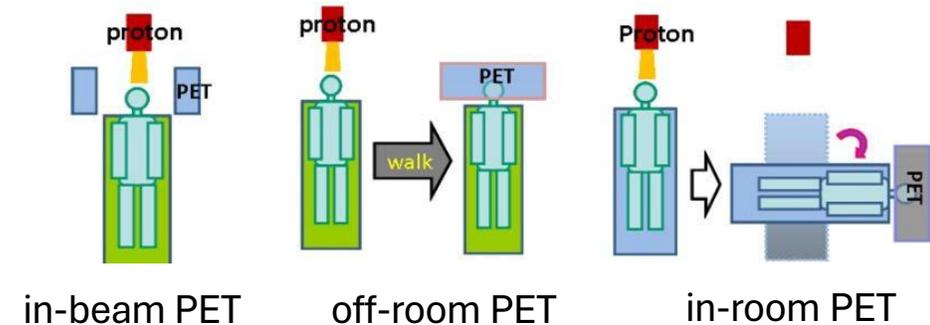


Positron Emitters

J Pawelke et al., Proceedings IBIBAM, 26.-29.09.2007, Heidelberg

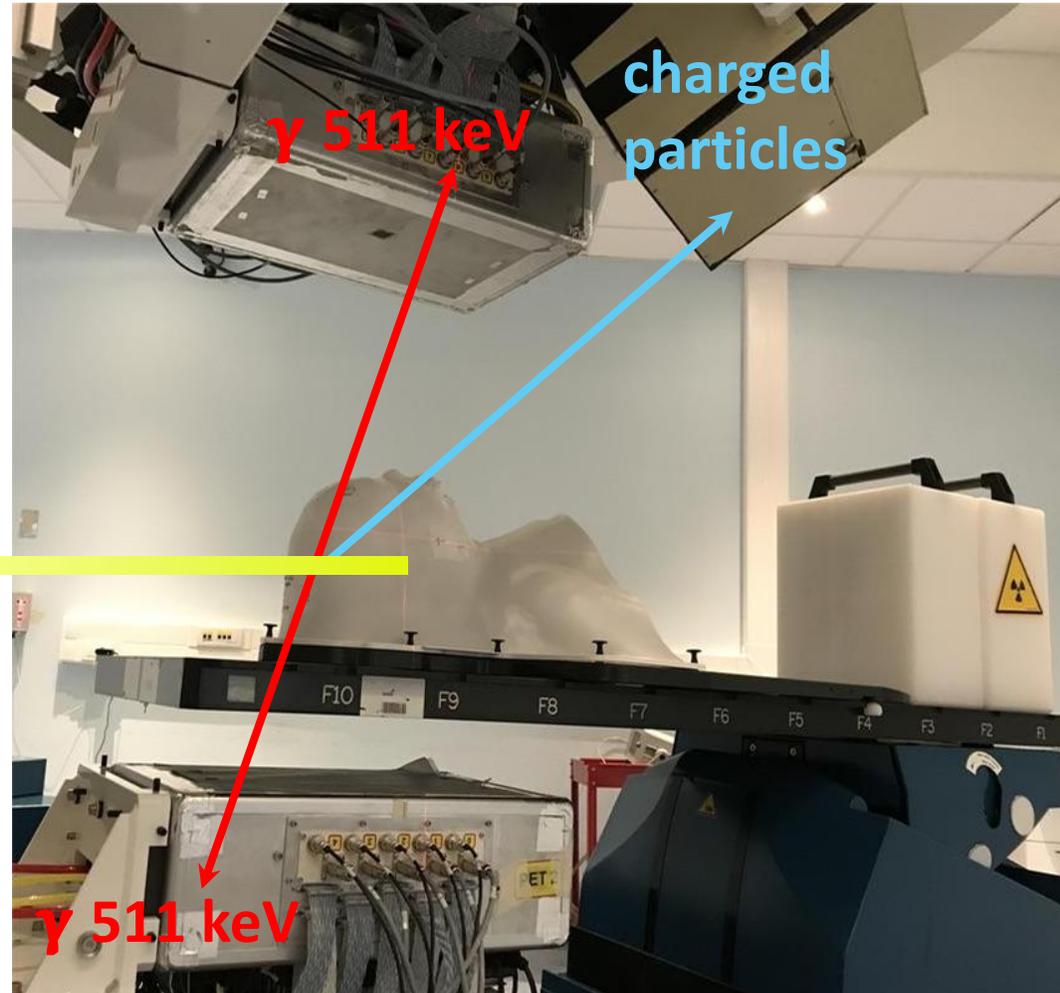
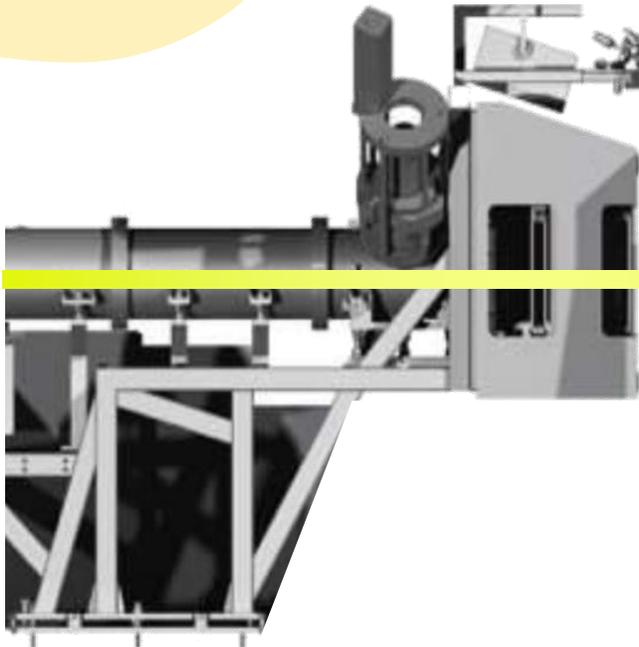


Isotope	T _{1/2}	Isotope	T _{1/2}	Isotope	T _{1/2}
^{15}O	2.037 min	^{30}P	2.498 min	^8B	770 ms
^{11}C	20.385 min	^{38}K	7.636 min	^{12}N	0.011 s
^{13}N	9.965 min	^9C	126.5 ms	^{13}O	8.58 ms

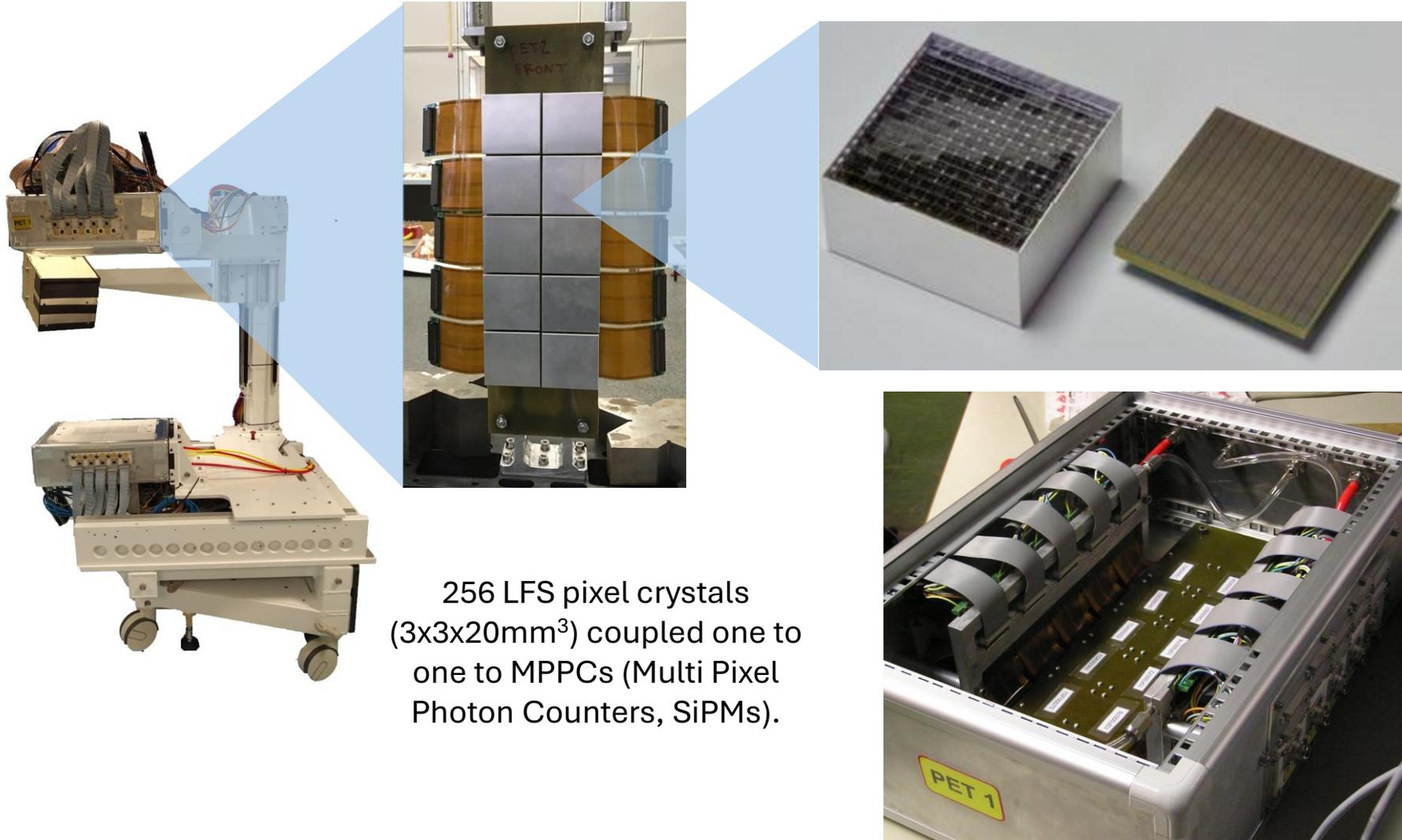


The INSIDE system

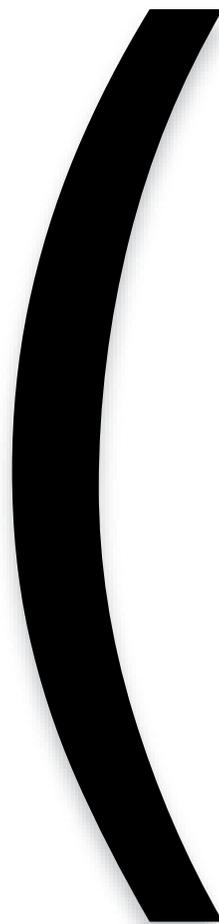
INSIDE is a bimodal system



In-beam PET



256 LFS pixel crystals ($3 \times 3 \times 20 \text{mm}^3$) coupled one to one to MPPCs (Multi Pixel Photon Counters, SiPMs).

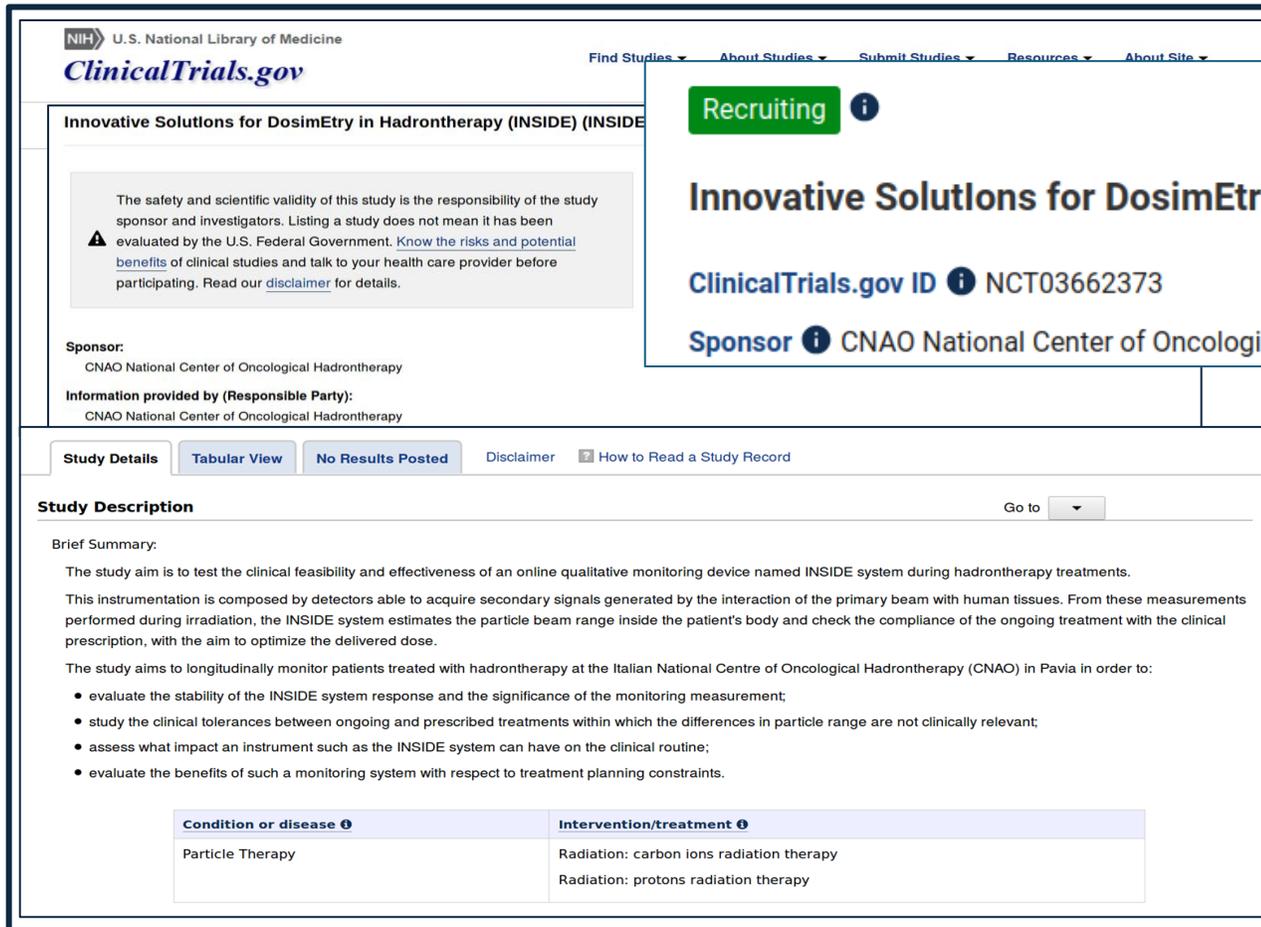


Mechanics



Documentation, safety, etc

- Ethics Committee/review board approval
- Safety compliance – electrical, mechanical etc
- Training of the personnel
- Clinical workflow integration



The screenshot shows the ClinicalTrials.gov website for the trial "Innovative Solutions for Dosimetry in Hadrontherapy (INSIDE) (INSIDE)". The page includes a "Recruiting" status badge, the ClinicalTrials.gov ID NCT03662373, and the sponsor CNAO National Center of Oncological Hadrontherapy. A disclaimer states that the safety and scientific validity of the study is the responsibility of the sponsor and investigators. The study description section includes a brief summary and a table of conditions and interventions.

Recruiting ⓘ

Innovative Solutions for Dosimetry in Hadrontherapy (INSIDE) (INSIDE)

ClinicalTrials.gov ID ⓘ NCT03662373

Sponsor ⓘ CNAO National Center of Oncological Hadrontherapy

Study Details | **Tabular View** | No Results Posted | Disclaimer | How to Read a Study Record

Study Description Go to ▾

Brief Summary:

The study aim is to test the clinical feasibility and effectiveness of an online qualitative monitoring device named INSIDE system during hadrontherapy treatments. This instrumentation is composed by detectors able to acquire secondary signals generated by the interaction of the primary beam with human tissues. From these measurements performed during irradiation, the INSIDE system estimates the particle beam range inside the patient's body and check the compliance of the ongoing treatment with the clinical prescription, with the aim to optimize the delivered dose.

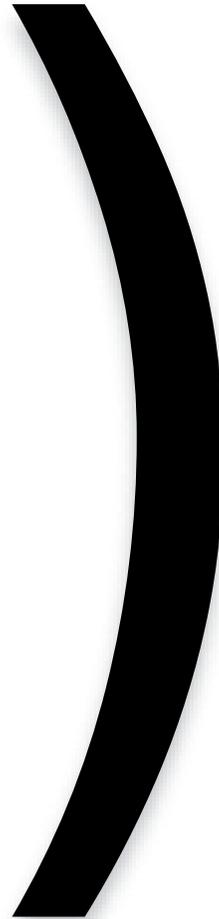
The study aims to longitudinally monitor patients treated with hadrontherapy at the Italian National Centre of Oncological Hadrontherapy (CNAO) in Pavia in order to:

- evaluate the stability of the INSIDE system response and the significance of the monitoring measurement;
- study the clinical tolerances between ongoing and prescribed treatments within which the differences in particle range are not clinically relevant;
- assess what impact an instrument such as the INSIDE system can have on the clinical routine;
- evaluate the benefits of such a monitoring system with respect to treatment planning constraints.

Condition or disease ⓘ	Intervention/treatment ⓘ
Particle Therapy	Radiation: carbon ions radiation therapy Radiation: protons radiation therapy

Observational clinical trial
40 patients (head-and-neck pathologies):

- Phase I: 20 patients enrolled between 2019 July and 2020 February
- Phase II: 20 patients, enrollment ongoing from 2024 November

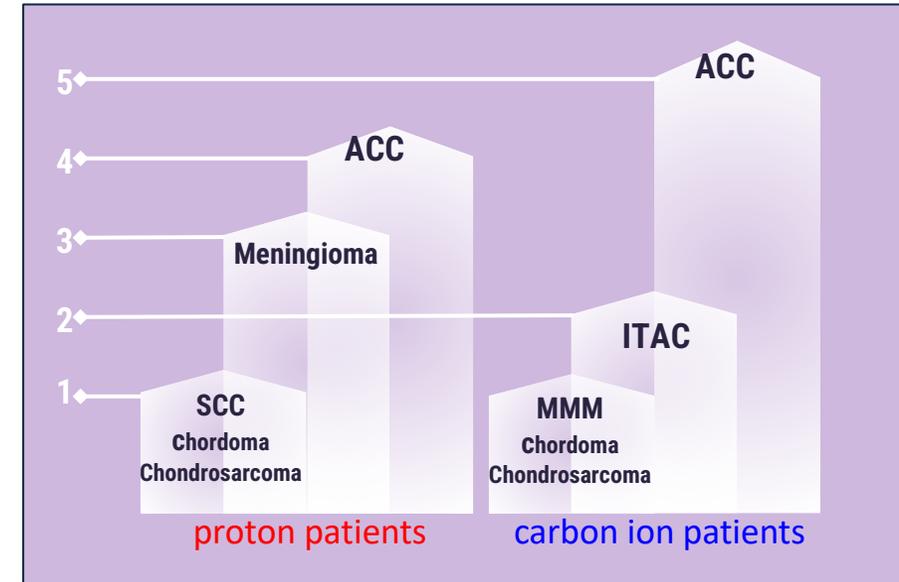


Clinal trial phase I



- 1) Evaluate the INSIDE sensitivity in a clinical environment
- 2) Test the INSIDE capability to detect interfractional morphological changes

- 3-5 patients/day
- Acquisition schedule: 2/3 consecutive days /week
- Patient monitoring during the fractions corresponding to control CTs
- Wide range of pathologies
- No mechanical issues or problems during acquisitions, effectiveness of the compatibility test in the treatment room
- Emergency procedure effective when necessary

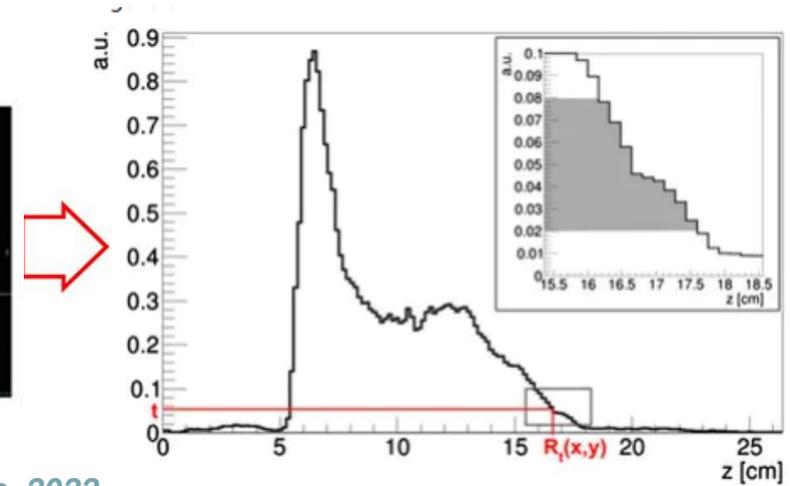
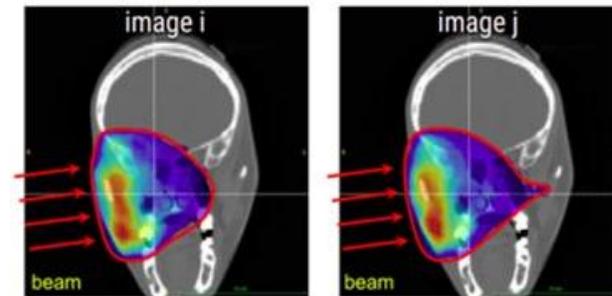
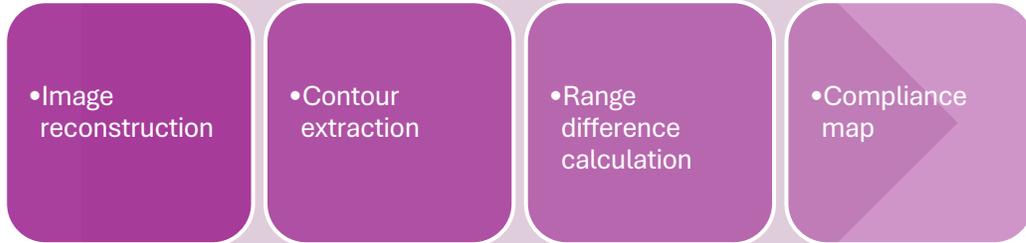
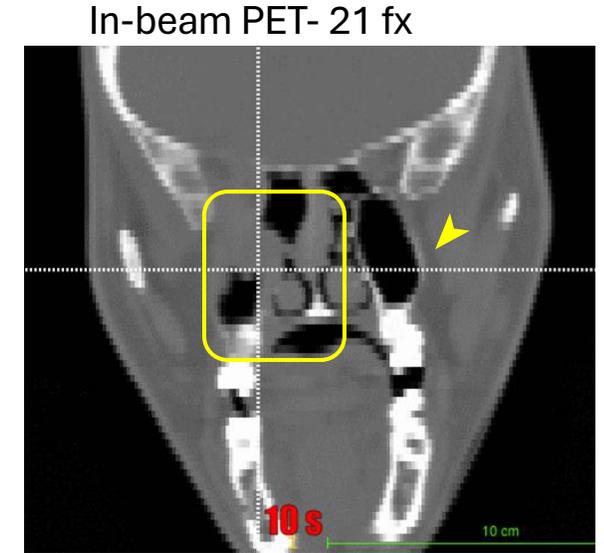
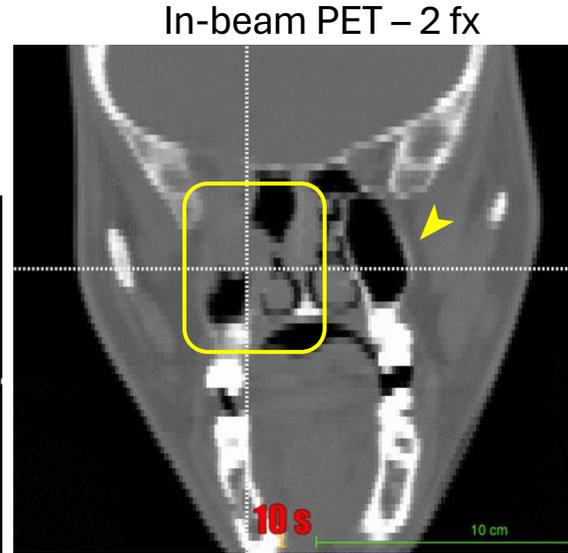
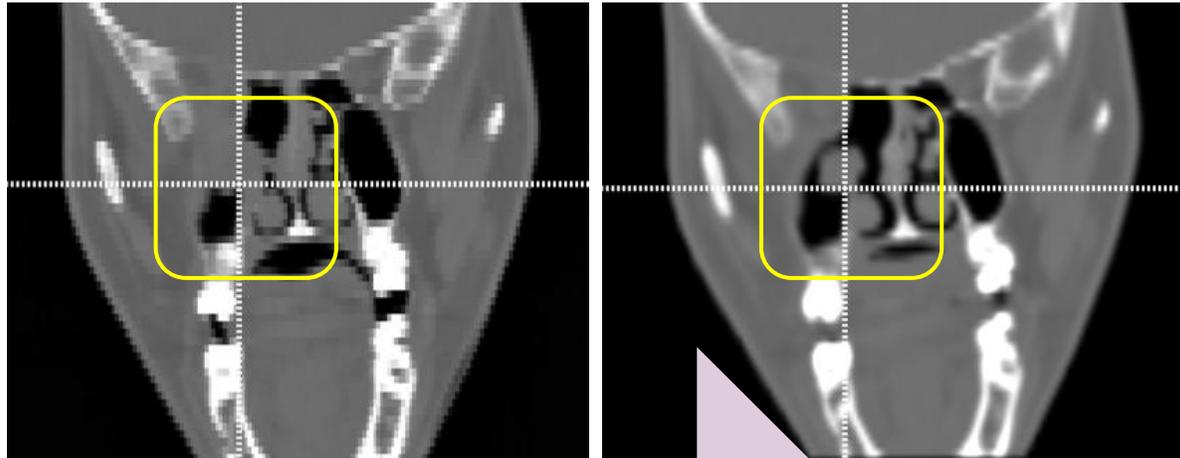


5 monitored patients underwent interfractional morphological changes (2 protons, reduction observed, 3 carbon ions)

2 patients needed replanning (C, ITAC, tumour growth before treatment)

INSIDE clinical trial I

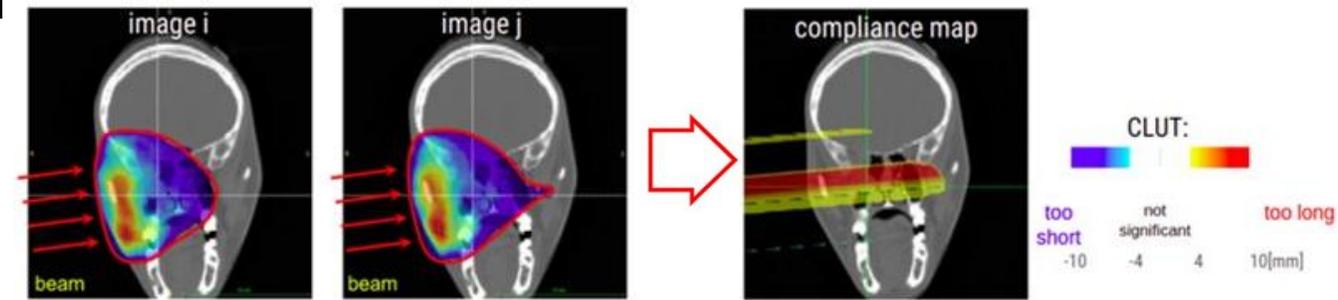
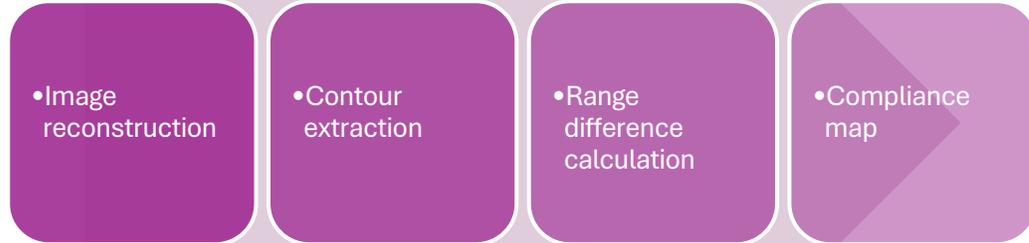
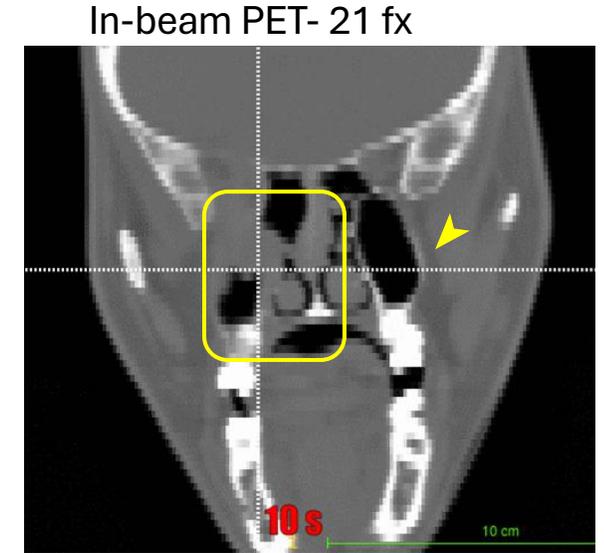
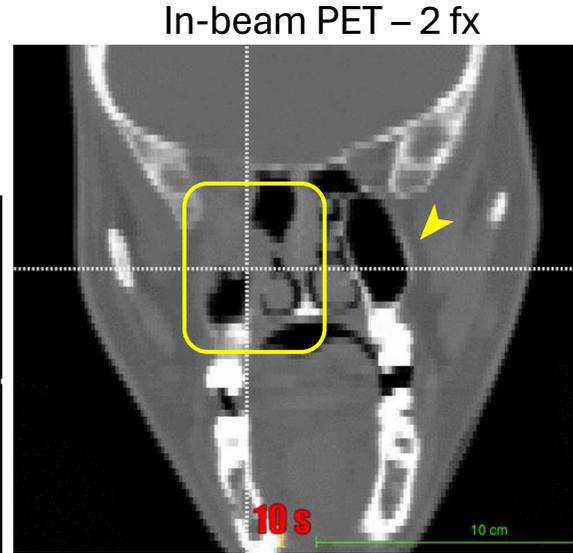
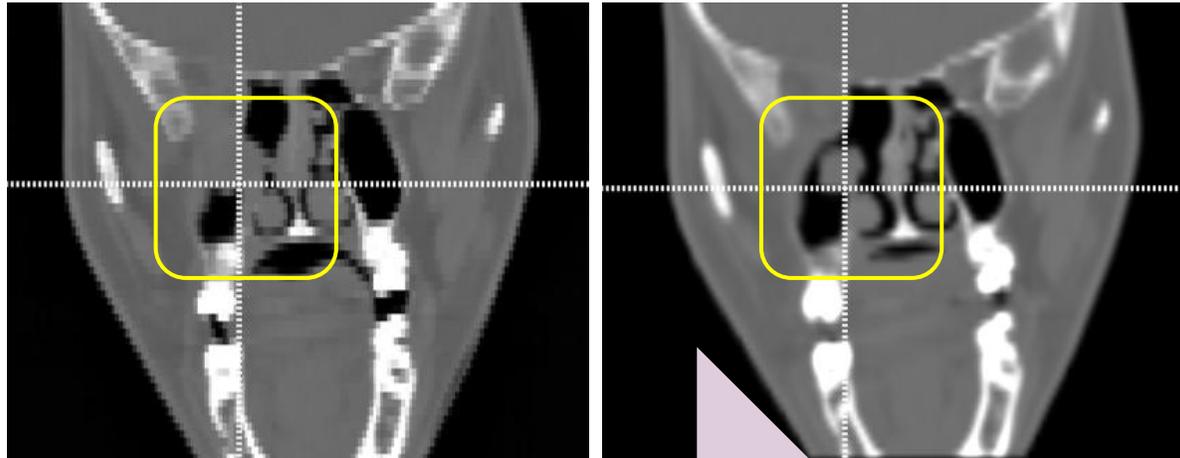
Patient ID: 006P: female, 39y, affected by ACC, IMPT, CTV dose: 70 GyE in 35 fx (2.0 GyE/fx, 5 fx/week), two beams (15° - 175° IEC) planning CT control CT - 20 fx



Fiorina et al., Fron. Phys., 2021; Moglioni et al., Front. Onc. 2022

INSIDE clinical trial I

Patient ID: 006P: female, 39y, affected by ACC, IMPT, CTV dose: 70 GyE in 35 fx (2.0 GyE/fx, 5 fx/week), two beams (15° - 175° IEC) planning CT control CT - 20 fx



Morphological changes detected!

Fiorina et al., Fron. Phys., 2021; Moglioni et al., Front. Onc. 2022

INSIDE clinical trial II

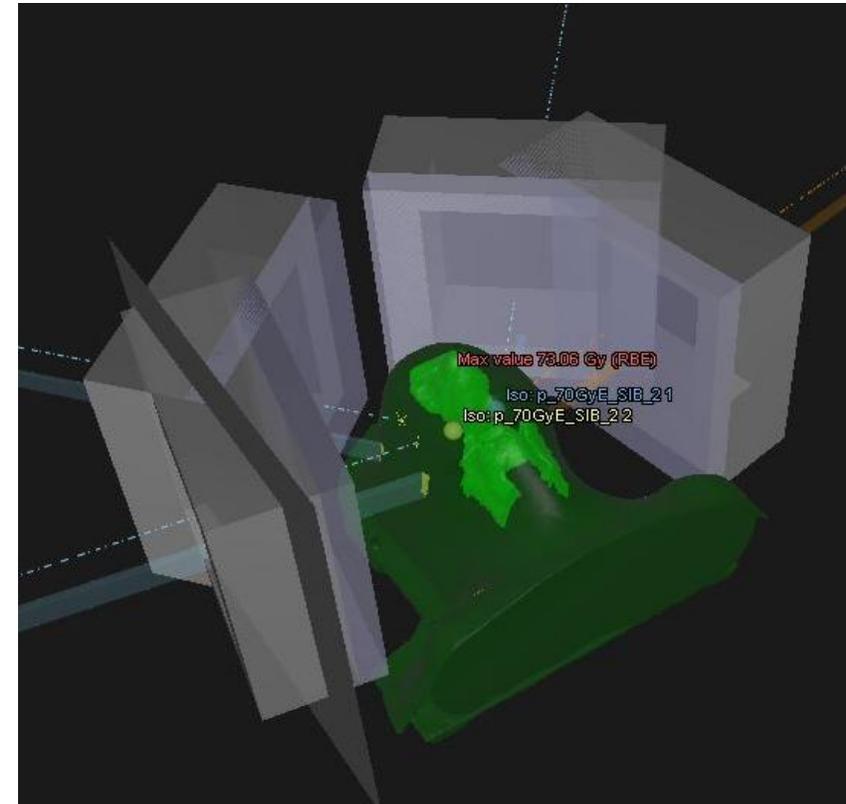


Assess the INSIDE capability to detect interfractional morphological changes

Phase II

- 2-3 patients/day
- Acquisition schedule: **the main treatment (about 30 fx protons, 9 fx carbon ions) is monitored. 3 consecutive days /week for protons, all fractions for carbon ions.**
- Patient monitoring during the fractions corresponding to control CTs (fx 1-15-25 for protons and fx 1-9 for carbon ions)
- **Pathologies in which morphological changes may occur**, curative treatment, no previous surgical resection.

patients enrolled:
4 treated with protons
3 treated with carbon ions



Different treatment geometries in use wrt Phase I (e.g. usually 4 beam fields used with protons, large targets)

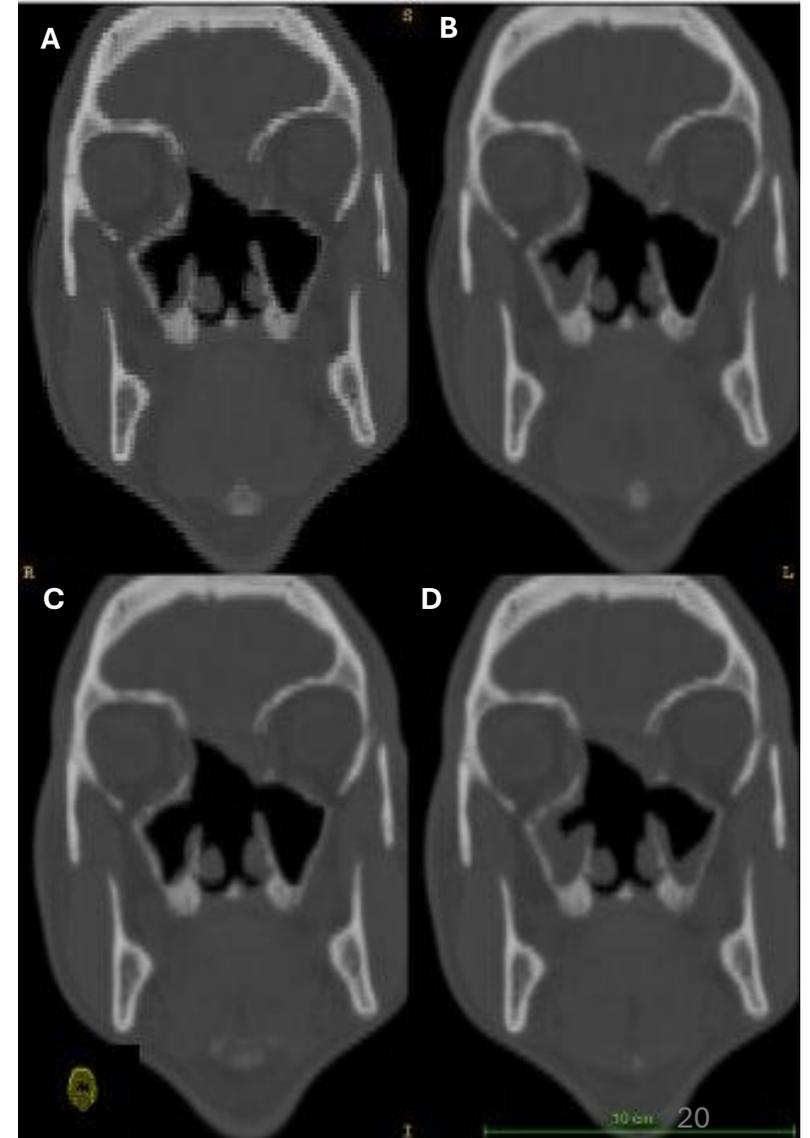
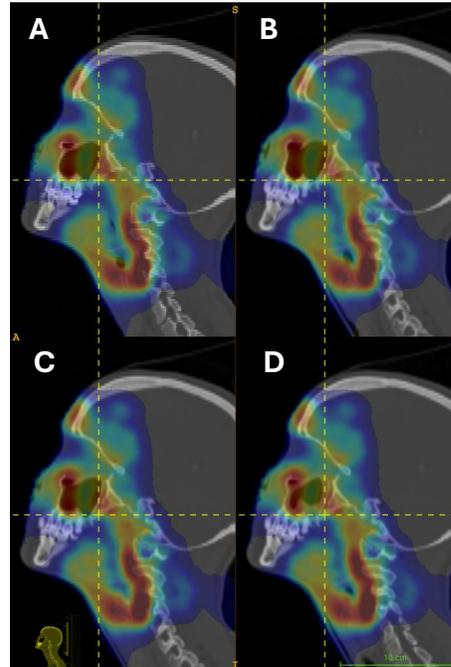
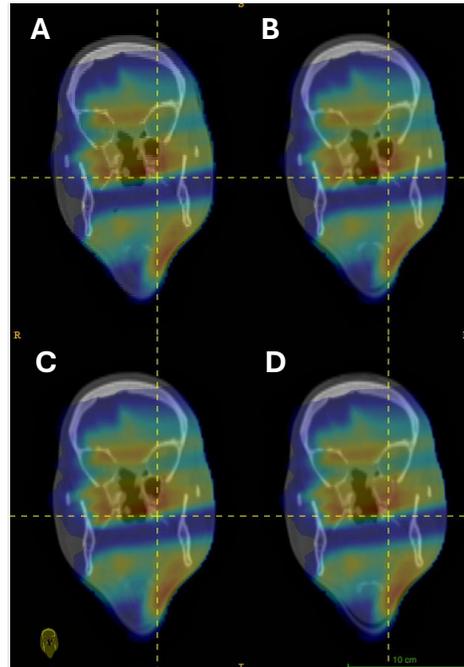
INSIDE clinical trial II

011P - Esthesioneuroblastoma

35 fractions – 5 days/week - CTVHD prescribed dose = 70 GyE

CTVLD including sinonasal cavities

First monitored field patient bed angle= 350° IEC coord.



Right cavity slightly filled, left cavity empty

Moderate filling of right cavity

Emptying of right cavity (similar to planning CT)

Severe filling of left and right cavities

A PLANNING CT
12/11/2025

B TREATMENT START
CONTROL CT
26/11/2025

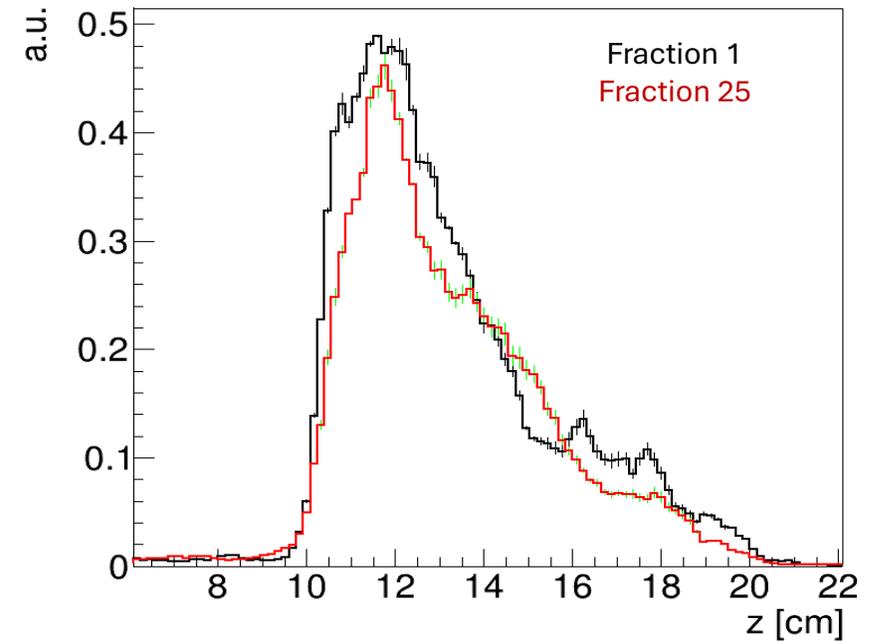
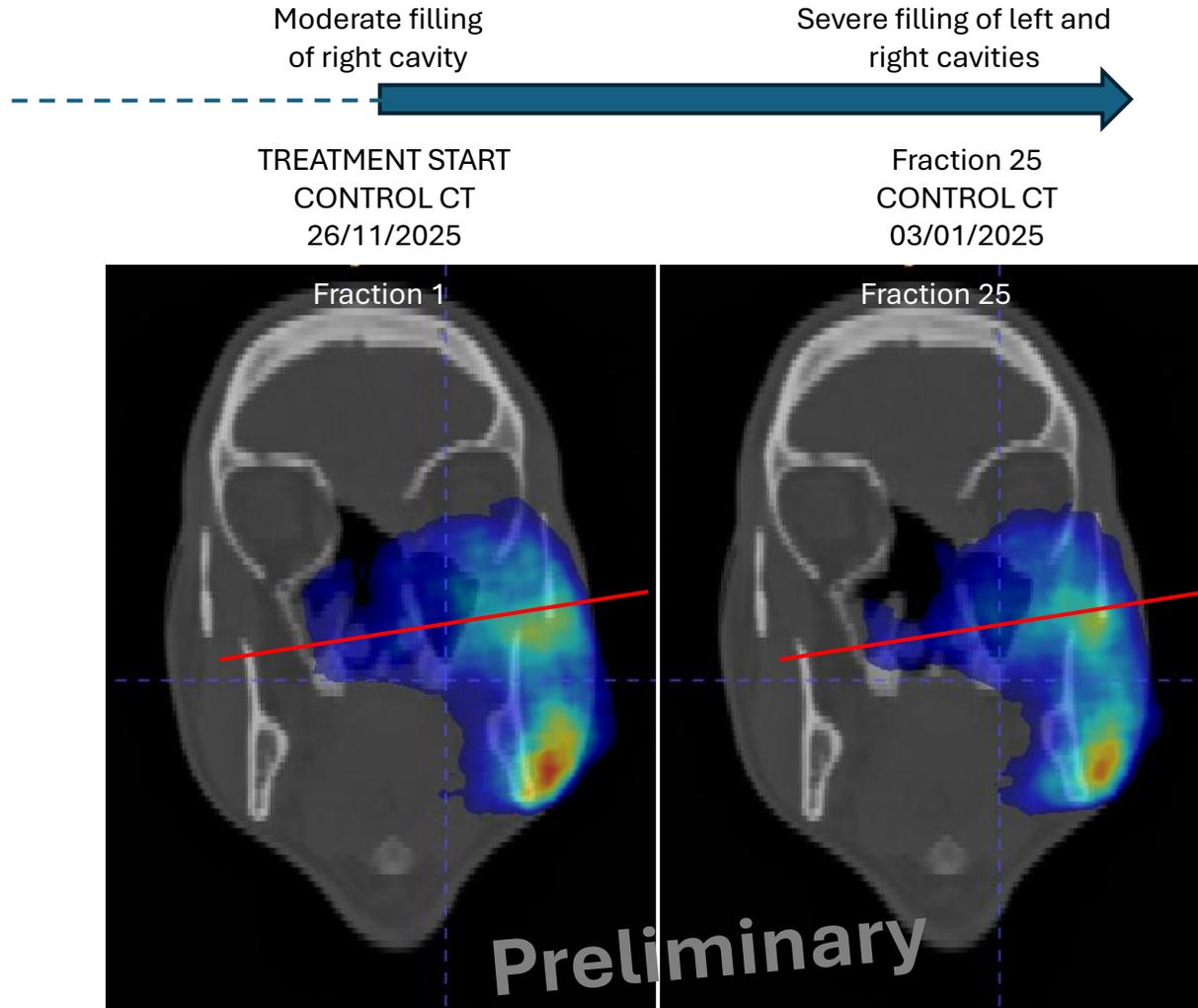
C Fraction 15
CONTROL CT
18/12/2024

D Fraction 25
CONTROL CT
03/01/2025

REPLANNING!

INSIDE clinical trial – preliminary

011P - Esthesioneuroblastoma



Compliance map is easy to interpret in the case of high statistics and changes in one single region.

- **When designing a new system, plan for Clinical Integration Early**
Anticipate workflow and patients-related constraints.
- **Keep in mind regulatory constraints**
- **INSIDE Clinical Trials: Lessons Learned**
 - **Trial I:** Demonstrated in-beam PET sensitivity for range verification.
 - **Trial II:** Boundary conditions matter!
- **Image Analysis:** Threshold selection impacts accuracy.
- **Treatment Geometry:** Irradiated volume size influences PET signal.

Acknowledgments

- Istituto Nazionale di Fisica Nucleare, sezioni di Torino, Pisa, Roma, Pavia – Italy
- Dipartimento di Fisica, Università di Pisa – Italy
- Centro Nazionale di Adroterapia Oncologica (CNAO) – Italy
- Università degli Studi di Torino – Italy
- Centro Fermi, Roma – Italy