Hadron therapy: developments in Italy

2nd COPIGAL WORKSHOP
on Studies of Exotic Nuclei
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OUTLINE

- Introduction to Charged Particle (or Hadron) Therapy

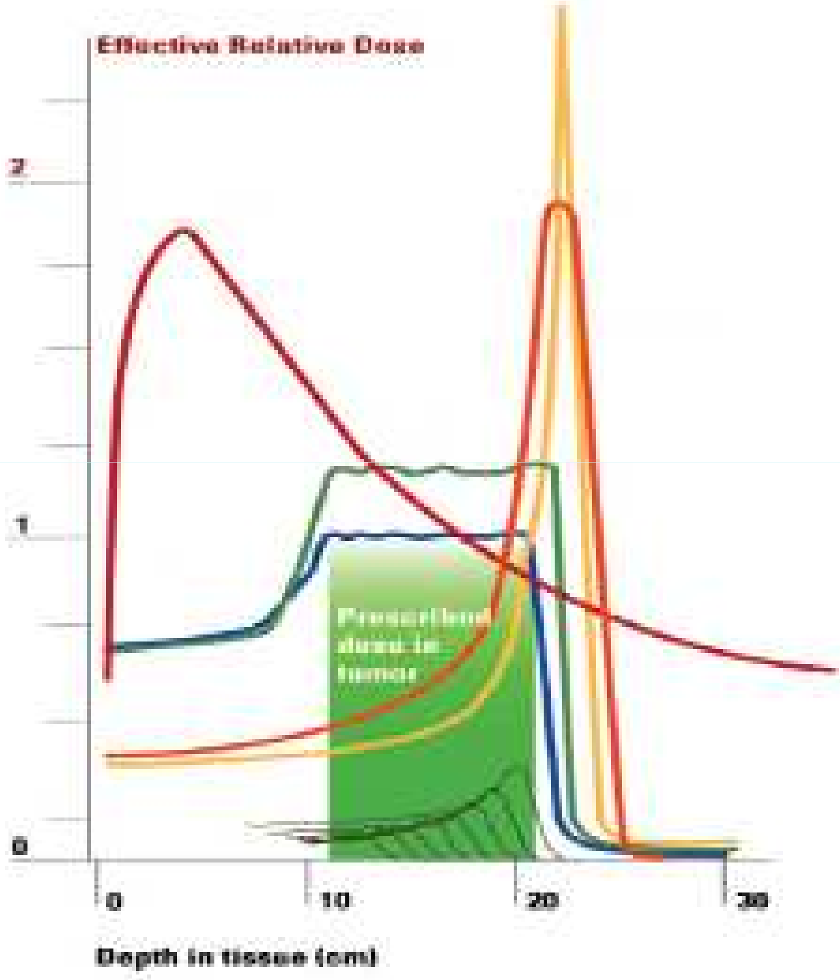
1. Basic principles
2. Dose distribution methods: passive vs. active
3. Radiobiology of protons and Carbon ions
4. Proton vs. Carbon
5. Accelerator types: cyclotron vs synchrotron
6. Treatment Planning System (TPS)

- Developments in Italy: centers (treating patients or under construction) and activities related

1. CATANA at Laboratori Nazionale del Sud (LNS)
2. Centro Nazionale di Adroterapia Oncologica (CNAO) in Pavia
3. ATREP in Trento
4. INFN activities: TPS

- Open problems and possible future developments

Introduction to Charged Particle (or Hadron) Therapy: Basic principles



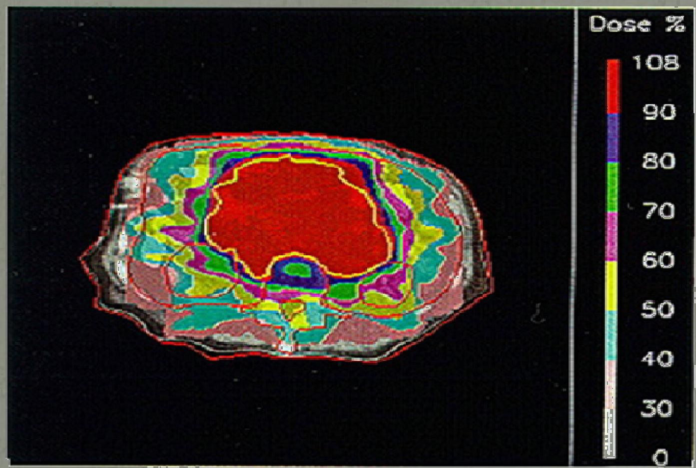
Dose-depth profiles

- Photons
- Protons
- Carbon ions
- SOBP with protons
- SOBP with Carbon

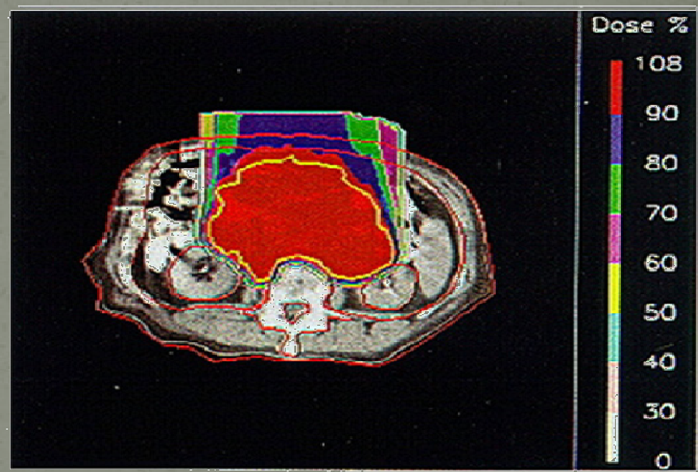
SOBP: Spread Out Bragg Peak

Hadrons: conformal irradiation

Abdomen



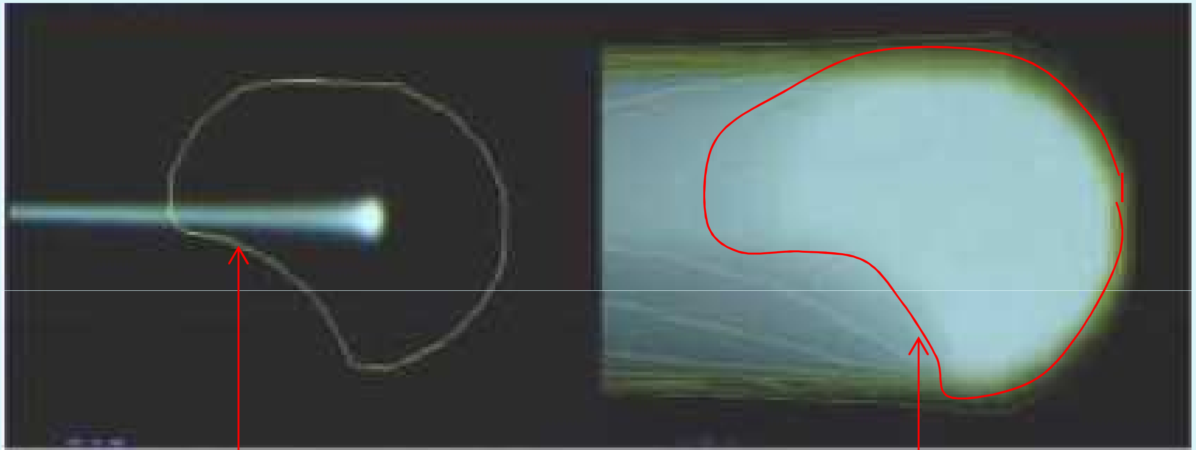
X-rays (IMRT) – 9 fields



Protons – 1 field

Courtesy of S. Rossi (CNAO)

Introduction to Charged Particle (or Hadron) Therapy: Dose distribution methods



Single native beam
~ 10 mm diameter

Area to be treated

Dose distribution method can be:

a) **passive**
b) **active**

Introduction to Charged Particle (or Hadron) Therapy: Dose distribution methods

a) passive method: 1) it is necessary to enlarge the *pencil beam* transverse dimensions; 2) to spread the energy, and 3) to conform the enlarged beam in the transverse plane to the patient tumour shape : **done with passive elements**

b) active scanning: *pencil beam* is steered through the Planning Treatment Volume (PTV) by changing the spot to which it is pointing: in the transverse plane with a pair of dipole magnets and in the longitudinal direction by changing energy.

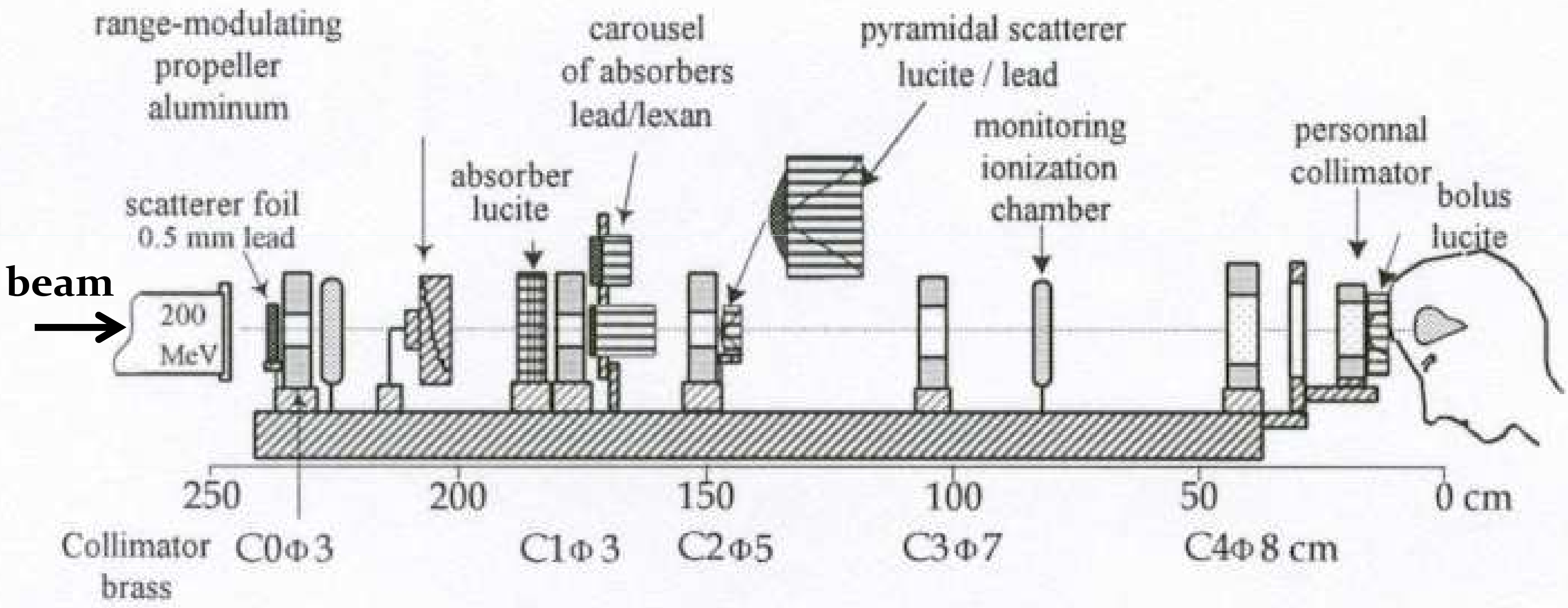
Active scanning: better conformance of the deposited dose to the PTV

For the clinical centers , there is a clear preference to go towards the:

Active scanning technique

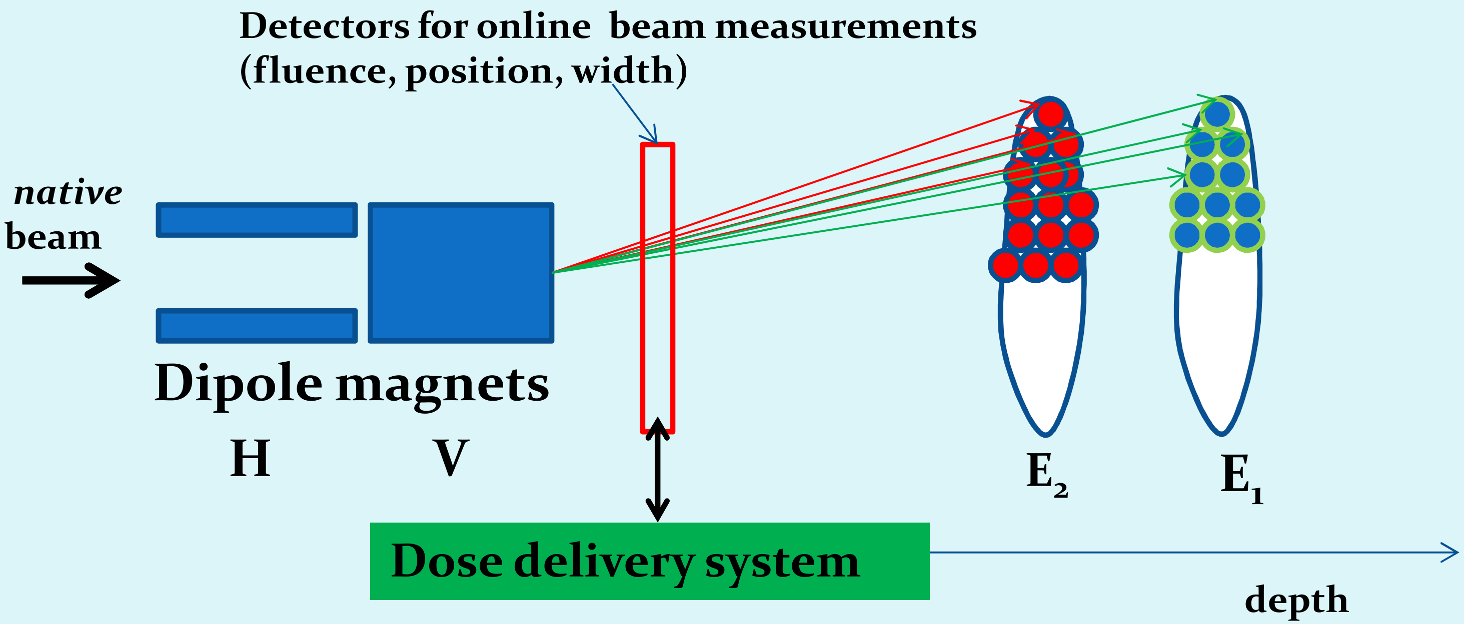
Introduction to Charged Particle (or Hadron) Therapy: Dose distribution methods

Passive method



Introduction to Charged Particle (or Hadron) Therapy: Dose distribution methods

Active method



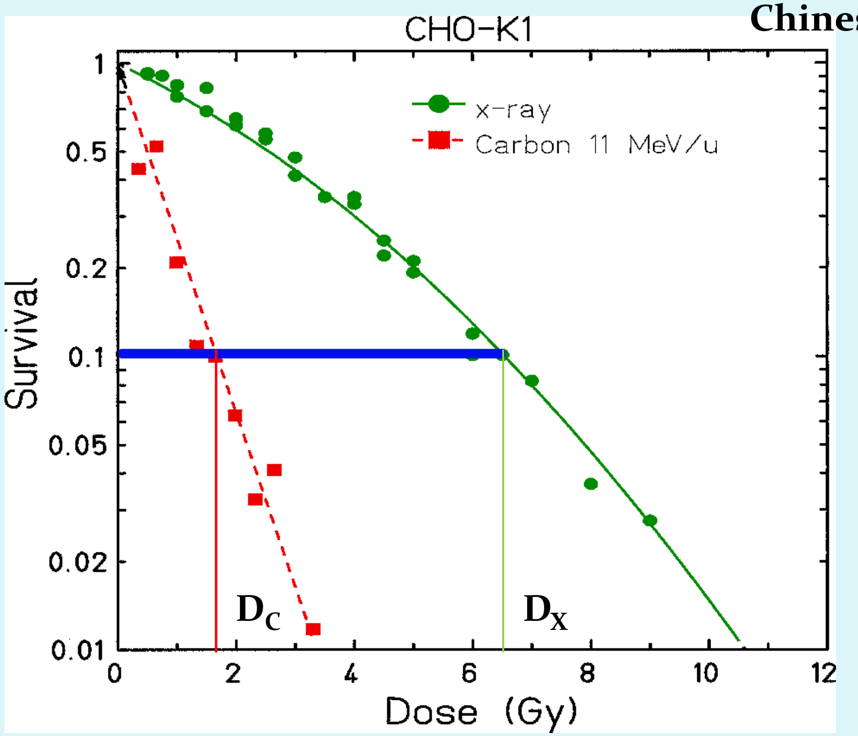
Treatment sequence

- *Paint* a iso-energetic slice
- change energy
- *paint* next slice
- *etc…*

Painting is done by modulating the dipole magnetic field along X and Y

Introduction to Charged Particle (or Hadron) Therapy: Radiobiology of Protons and Carbon ions

- Proton and/or light ion beams have a radiobiological impact stronger than the standard radiotherapy radiation (photons/electrons)
- The effect is described by the quantity known as RBE (Relative Biological Effectiveness)



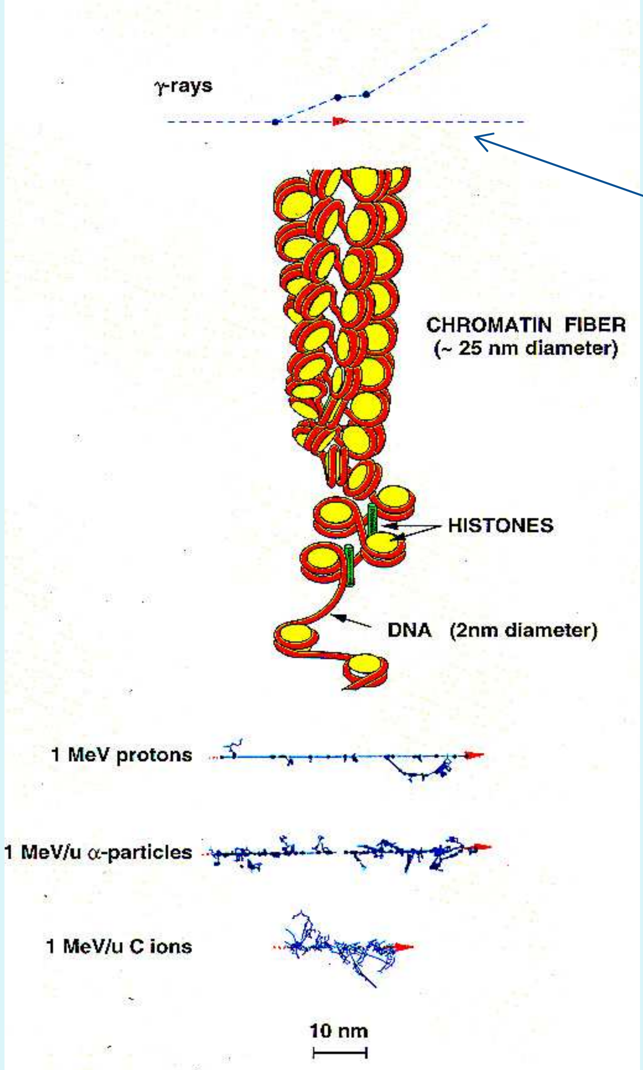
Chinese Hamster Ovary

$$RBE\Big|_{S=0.1} = \frac{D_X}{D_C} = \frac{6.5}{1.8} = 3.6$$

WK Weyrather, G Kraft - Radiother Oncol. 73-2 (2004)

RBE is a function of the beam energy, depth, cell line.
It needs to be modeled: Local Effect Model - LEM(GSI,De), Micro -dosimetric Kinetic Model - MKM

Introduction to Charged Particle (or Hadron) Therapy: Radiobiology of protons and Carbon ions



The different impact in breaking the DNA helix (double strand break) can be understood by comparing the energy release of :

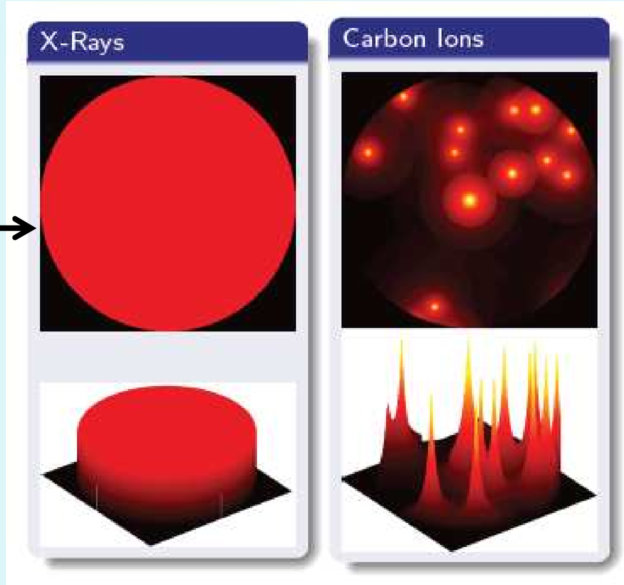
a) photons

b) Proton

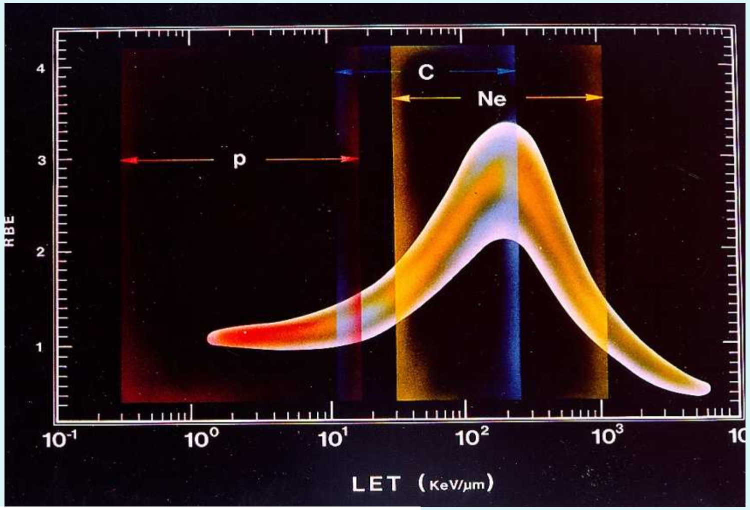
c) α– particles

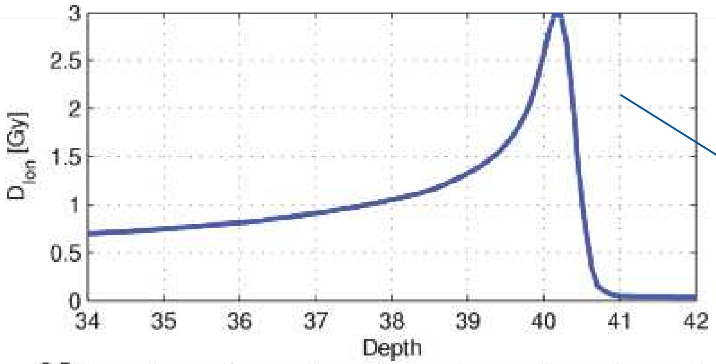
d) Carbon ions

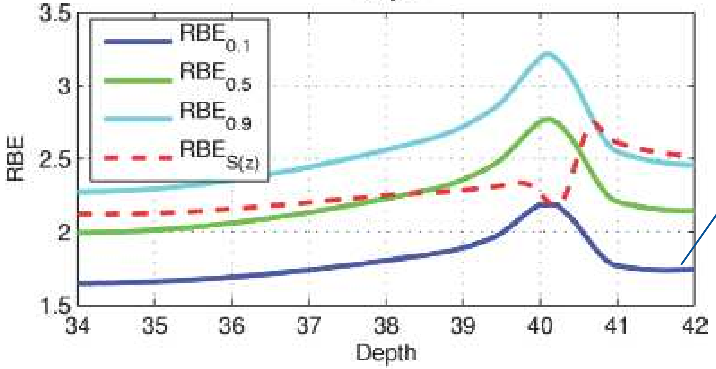
Comparison of the dose distribution for the same average dose of Photons and Carbon



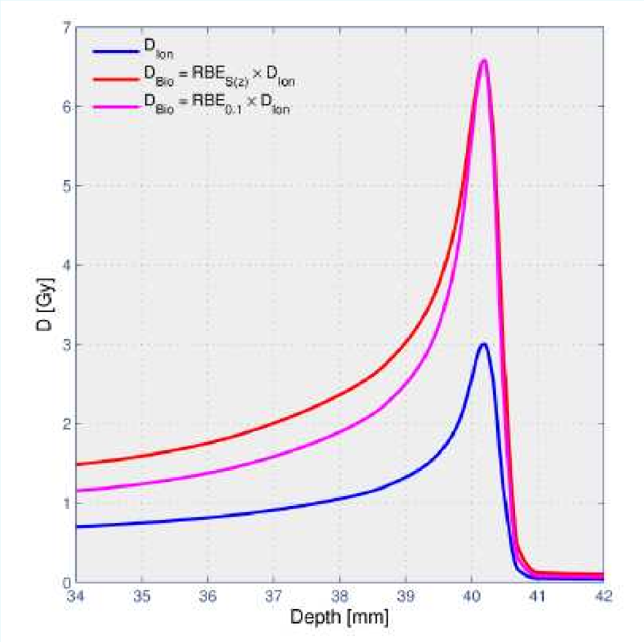
RBE vs LET







D_{eq} = RBE * D_{phys}



If you want to buy/build a center the main decisions to be taken are:

protons	vs	protons/carbon ion
active (spot scanning)	vs	passive scanning
cyclotron	vs	synchrotron

Introduction to Charged Particle (or Hadron) Therapy
Protons vs. Carbon ions

- At present the RBE for Protons is assumed to be constant (= 1.1-1.2) along the all depth. Some studies point to an increase at the very end of the Proton path. (Effect under study)
- RBE for Carbon ions is maximum at the Bragg peak and tends to favour the equivalent dose ratio between SOBP and entrance dose.
- Carbon more effective for hypoxic and radio-resistant tumors
- Carbon beam profile in the transverse plane is much more unalterable -> better penumbra
- Carbon produces fragments which can travel long distances, specially the very light ones as protons and alphas.
- Proton accelerators are smaller than Carbon ion accelerators -> cost less ! Proton energy < 250 MeV Carbon energy < 400 MeV

- Only clinical studies can address which is the best solution
- Not to forget intermediate ion species as Lithium

Introduction to Charged Particle (or Hadron) Therapy
Cyclotron vs Synchrotron

Cyclotron

Extraction at fixed energy

- Much smaller (it can fit in a typical *clinical* room)
- Easier to operate
- Less energy consumption
- Low maintenance cost

Synchrotron

Beam delivered at variable energy

- Energy selection done by changing the machine set-up
- Less neutron productions
- Carbon ion beam

Other accelerator species are under study, one to mention is the *Cyclinac* under development by the Amaldi's team at CERN

Introduction to Charged Particle (or Hadron) Therapy

Disadvantages of the Charged Particle Therapy (CPT->Hadrontherapy), wrt standard radiotherapy, are mainly related to cost/logistics

- Quality Assurance of the treatments requires more complex operations (higher cost)
- patient positioning and control more elaborate (higher cost): ~1 mm precision
- more complex machine with respect to the traditional 6-24 MV electron LINAC (higher cost)

Introduction to Charged Particle (or Hadron) Therapy
Treatment Planning System

Input

Informazione 3D:

- CT, MRI, PET
- PTV, OARs

+ cell type

$\rightarrow$ **TPS** $\rightarrow$

Output

- $D(x,y,z)$
- $\mathrm{RBE}(x,y,z)$
- $\{\phi_i, E_{Ki}, \theta_i\}$

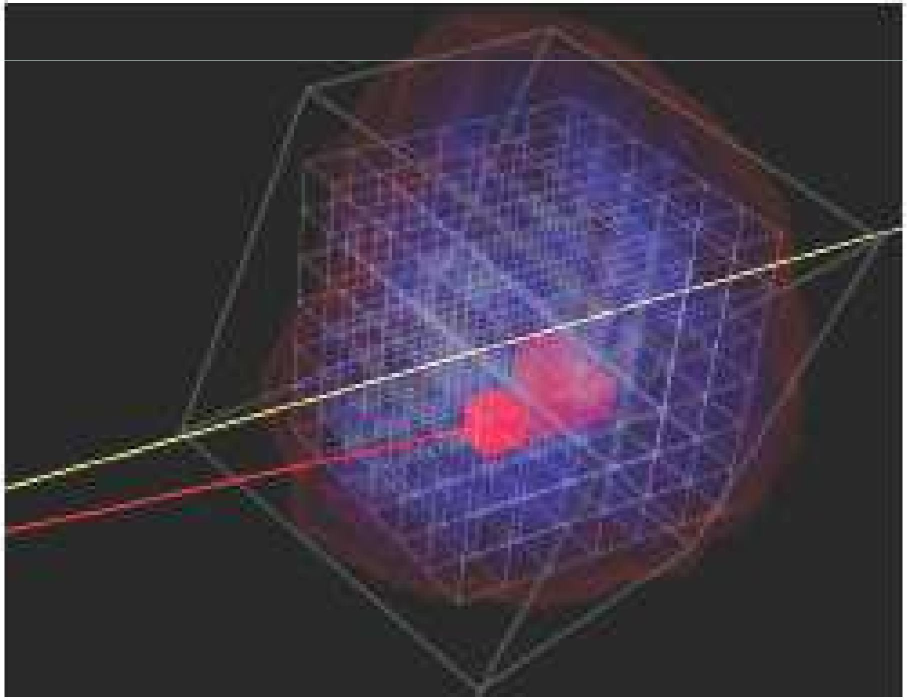
Voxel Scan:

$i \longrightarrow$ i-th beam **i = 10^4 - 10^5**

$\phi_i \longrightarrow$ fluence

$E_{Ki} \longrightarrow$ kinetic energy

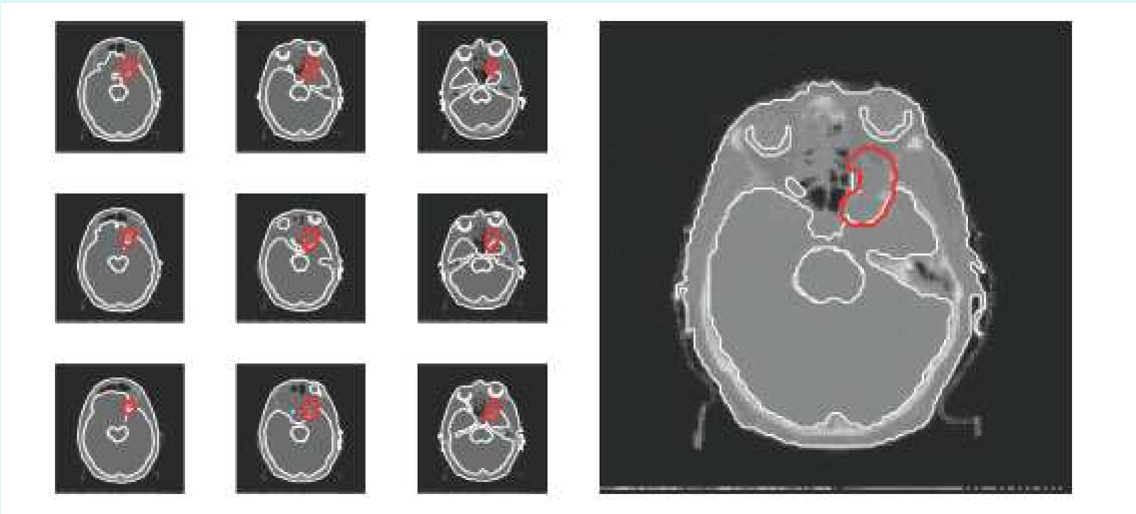
$\theta_i \longrightarrow$ direction



Treatment Planning System

As input to the TPS, it is necessary :

- patient anatomy information (from CT, MRI, or PET)
- the structure contouring of the Planning Target Volume (PTV) and Organ-at-Risk (OAR)
- the overall prescription: the Equivalent Dose and the fractioning
- field directions



Hadrontherapy in Italy: Number of potential patients

(Commission Ministry of Health – Year 2009)

ITALY: 60 MILLIONS HABITANTS

X-Ray therapy (photons 5 – 20 MeV)

New patients per year: 120'000 pts/y

Protons

Category A: elective patients = 1'000 pts/y

Category B: good indications = 12'000 pts/y

Carbon ions

radioresistant tumours = 1'500 pts/y

- 1 dual centre (p and C): CNAO -> 1500 pts/y
- possibly 1 protontherapy centre every 10 M citizens

Courtesy of S. Rossi- CNAO

Developments in Italy: centers (treating patients or under construction) and activities related

ELECTIVE INDICATIONS FOR PROTONTHERAPY IN ITALY			
Patology	**Patients per year**	**Potential patients for protons**	
		Patients per year	*Percentage to be treated with protons*
Uveal melanoma	310	310	100%
Chordoma of the skull base and spinal cord	45	45	100%
Chondrosarcoma of skull extremities and trunk	90	90	100%
Meningioma of skull base	250	125	50%
Paraspinal tumours	140	140	100%
Schwannoma of cranial nerves	300	45	15%
Adenoma of hypophysis	750	75	10%
Pediatric solid tumours	960	144	15%
TOTAL	**1885**	**974**	

Developments in Italy: centers (treating patients or under construction) and activities related

- CATANA at Laboratori Nazionali del Sud (LNS-INFN)

Cyclotron, protons, passive dose distribution

- CNAO (Pavia)

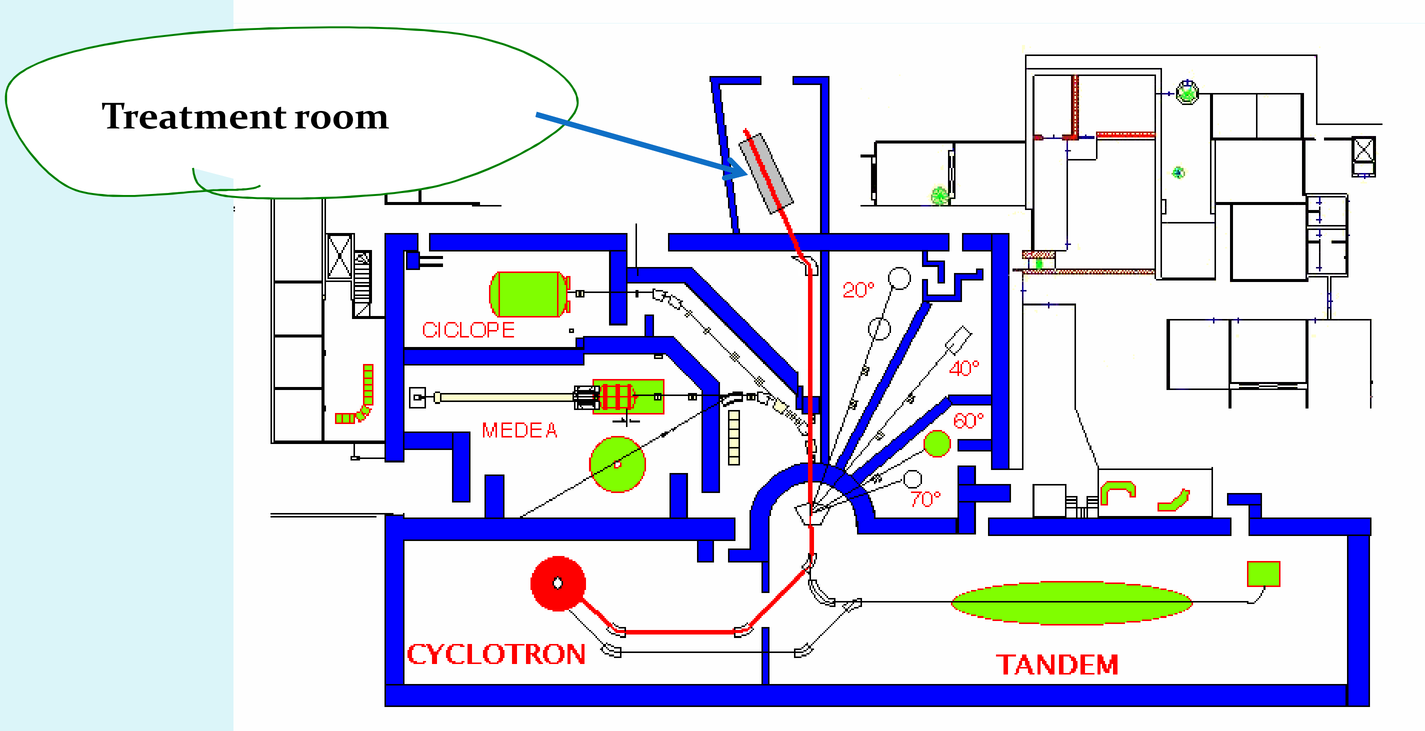
Synchrotron, proton and Carbon, active scan dose distribution

- ATreP (Trento) (under construction)

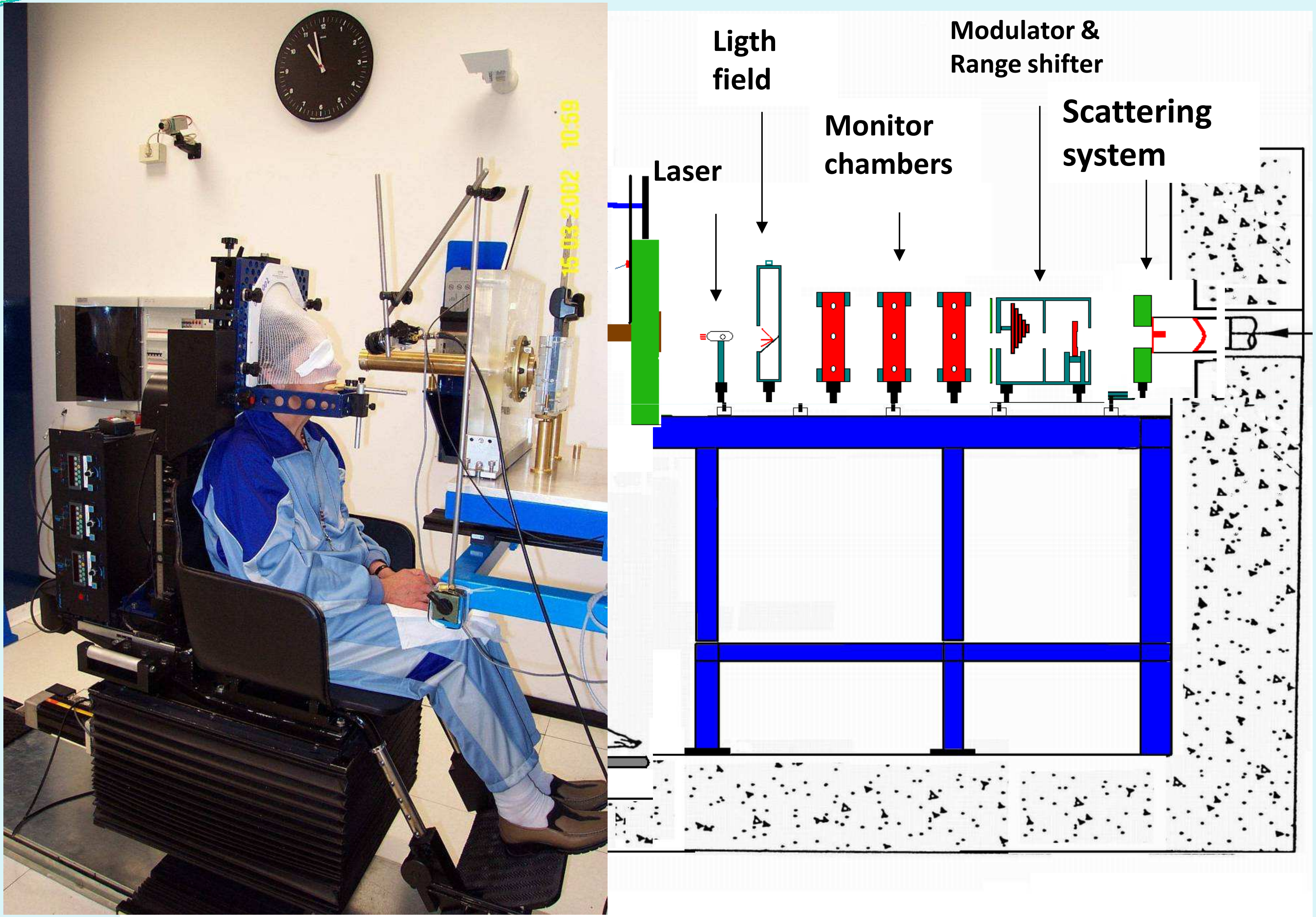
Cyclotron, protons, active scan dose distribution (IBA center)

Charged Particle Therapy in Italy: CATANA

- EYE PROTON THERAPY TREATMENTS, specifically:
- Treatment of the choroidal and iris melanoma
- In Italy about 300 new cases for year
- LNS Superconducting Cyclotron



CATANA beam line



G.A.P.Cirrone, cirrone@lns.infn.it

TREATMENT MODALITIES

Dose: 15.0 GE per day

Treatment Time: 45-60 sec.

Total Dose: 60 GE

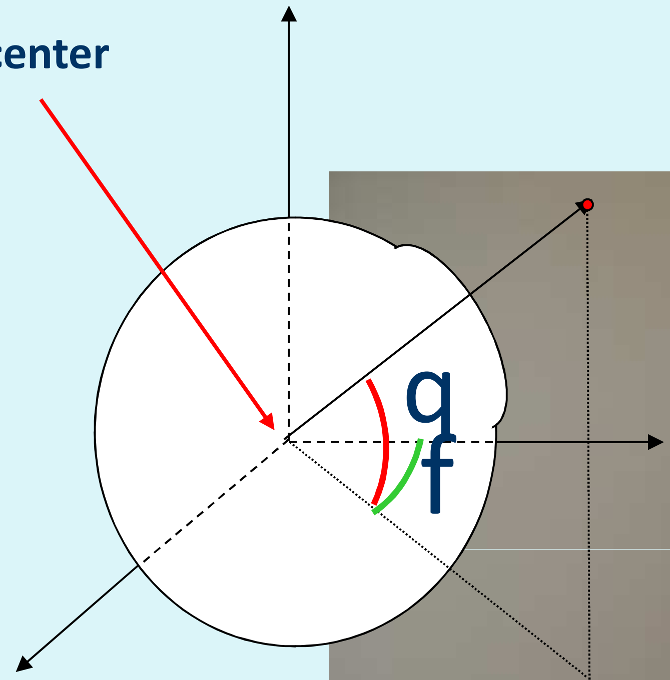
Fractions: 4

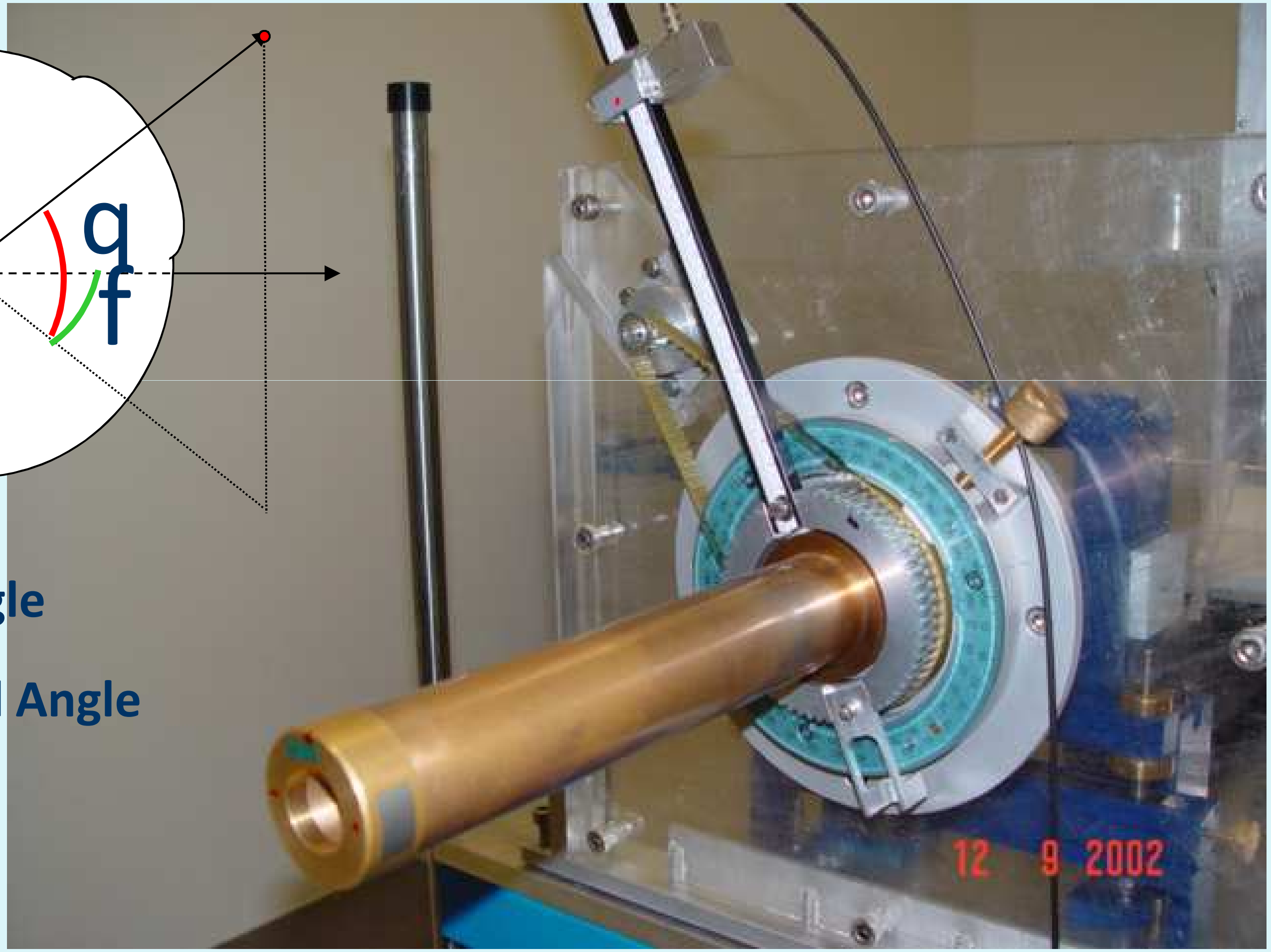
G.A.P.Cirrone, cirrone@lns.infn.it

TREATMENT PHASES

Isocenter

Fixation Light





q Polar Angle

f Azimuthal Angle

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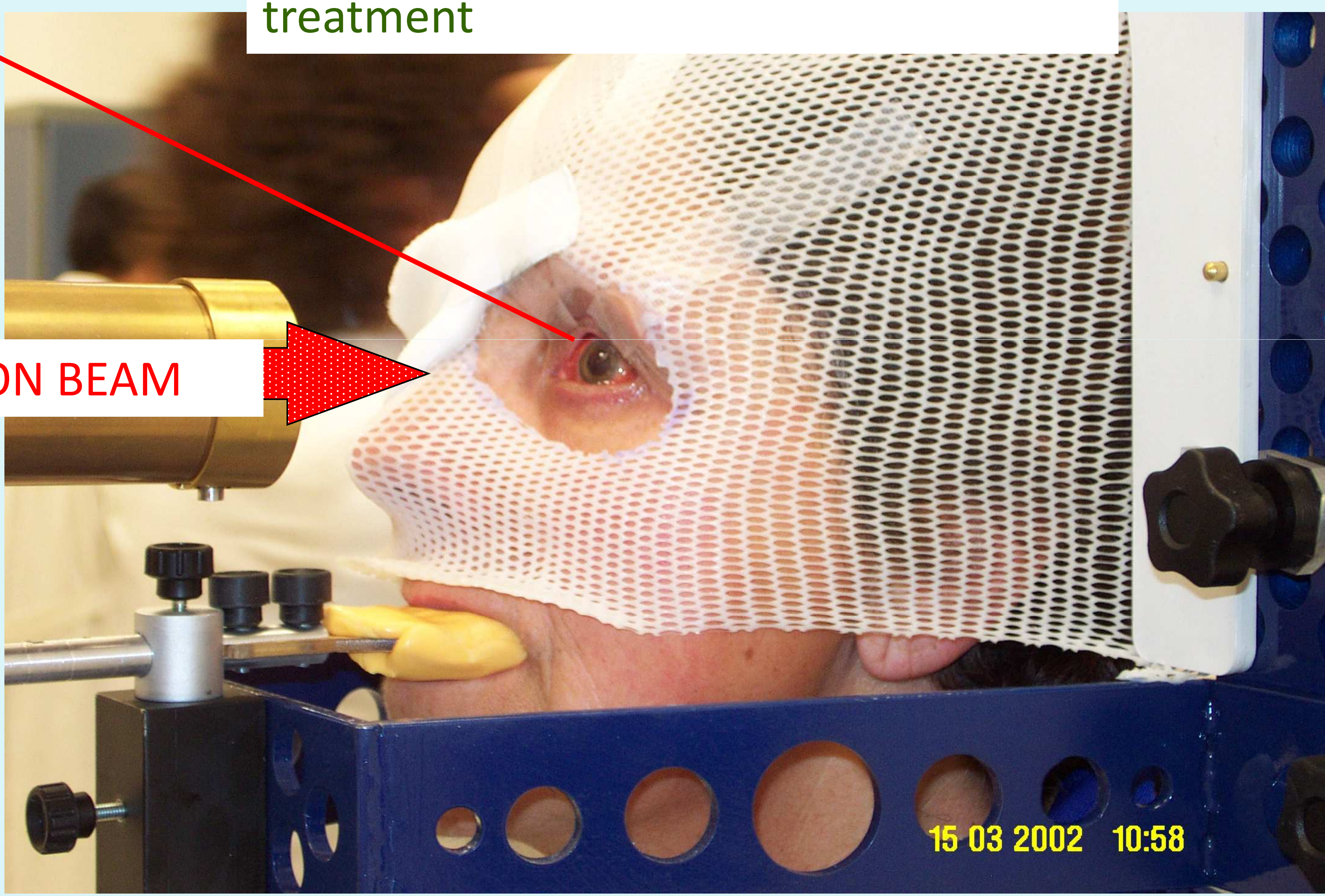
TREATMENT PHASES

Patiens look the fixation light during the treatment

PROTON BEAM



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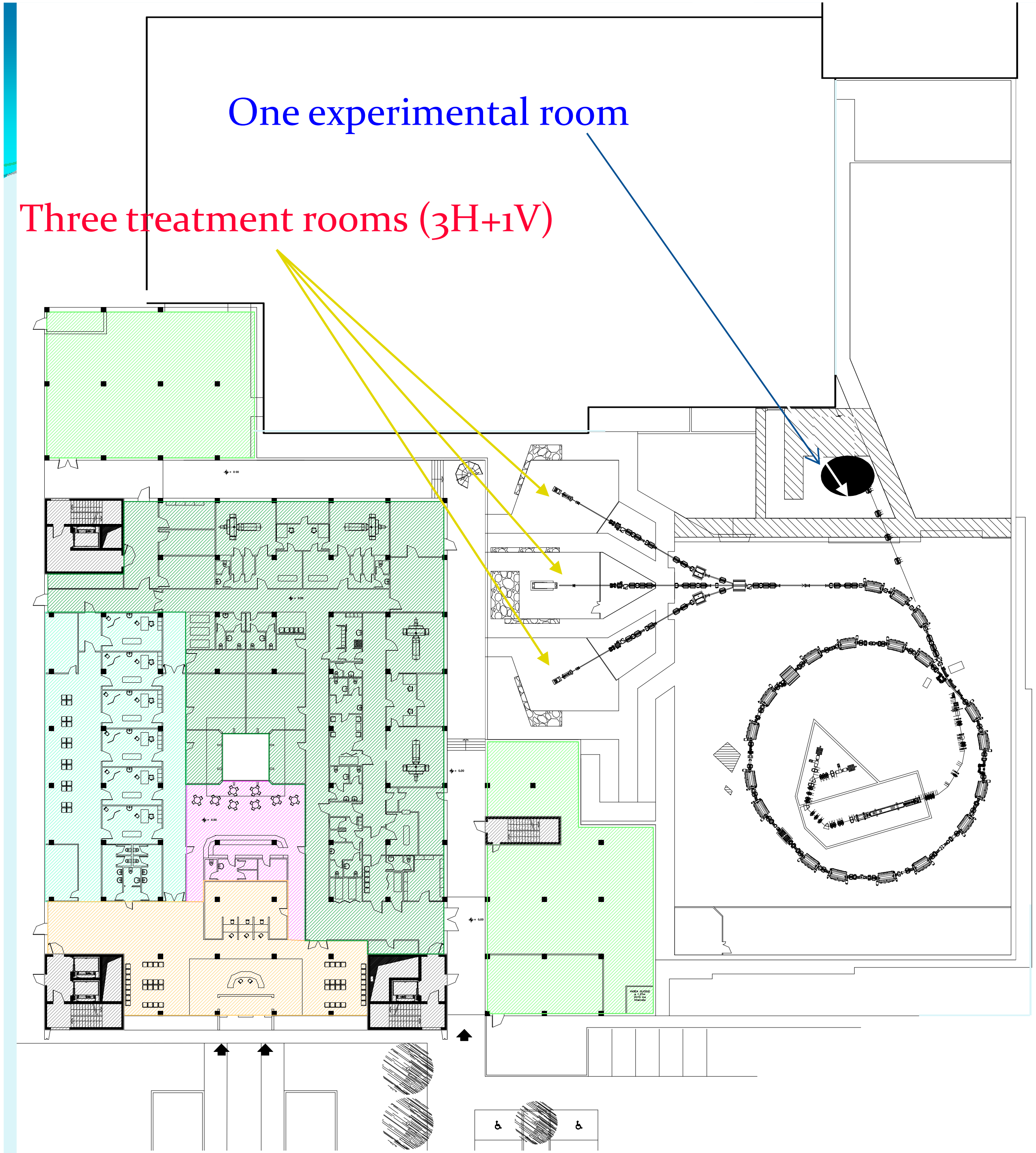
Status of the Charged Particle Therapy in Italy: **CNAO**

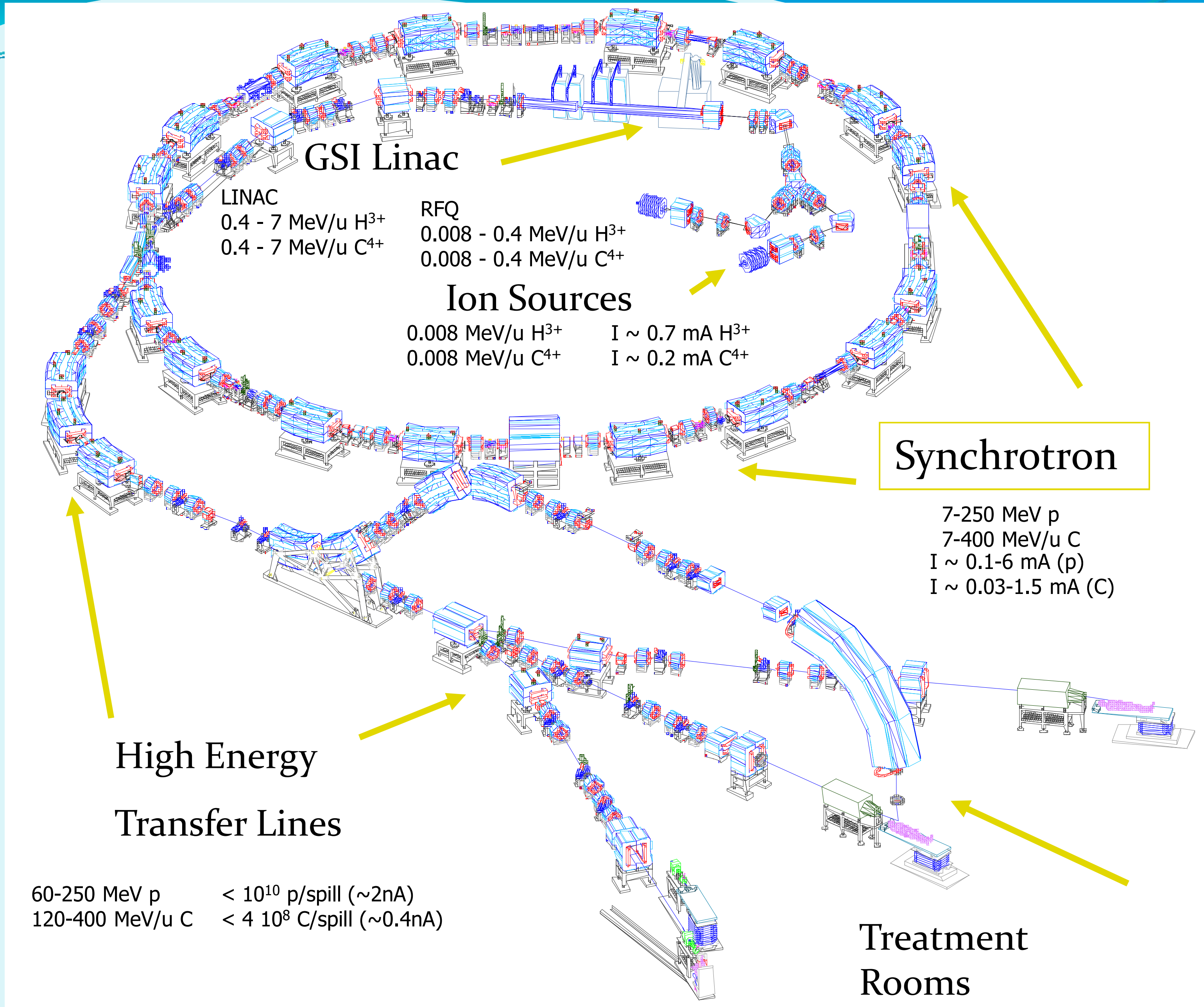
The CNAO has been completed end 2009

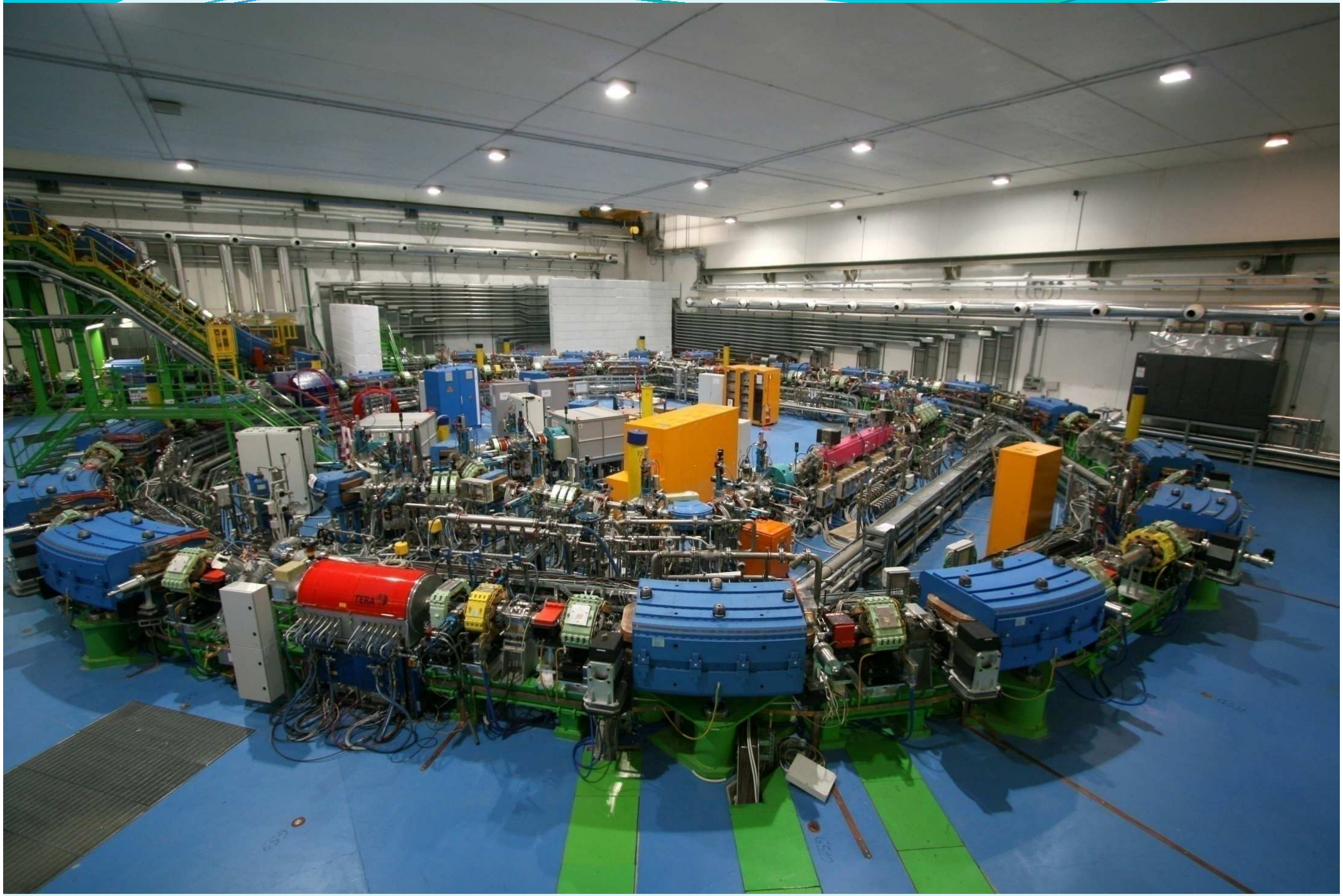
CNAO – Phase 1



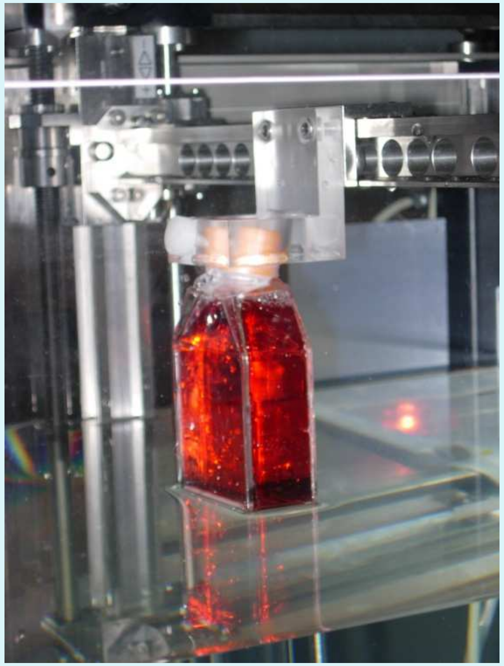
High precision devices for patient positioning

Courtesy of S. Rossi (CNAO)

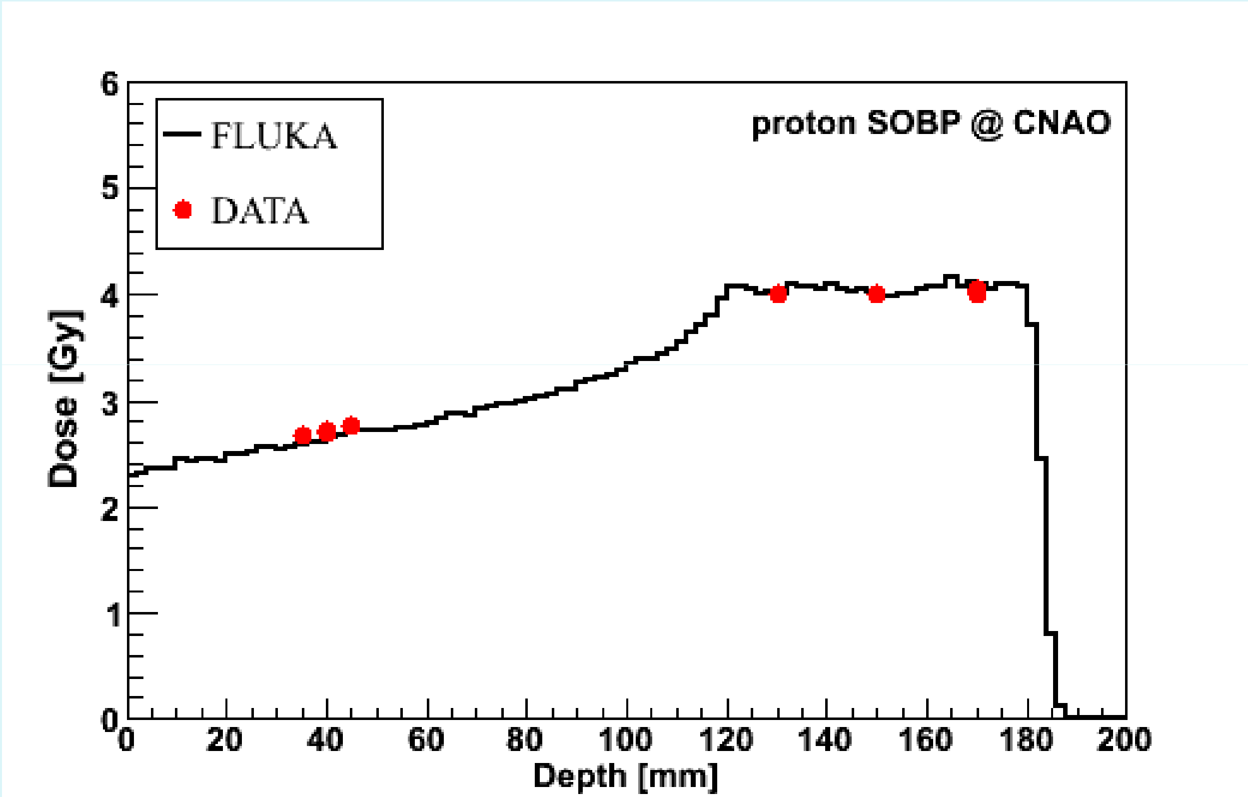

GSI Linac
LINAC
0.4 - 7 MeV/u H^{3+}
0.4 - 7 MeV/u C^{4+}
RFQ
0.008 - 0.4 MeV/u H^{3+}
0.008 - 0.4 MeV/u C^{4+}
Ion Sources
0.008 MeV/u H^{3+}
0.008 MeV/u C^{4+}
I ~ 0.7 mA H^{3+}
I ~ 0.2 mA C^{4+}
Synchrotron
7-250 MeV p
7-400 MeV/u C
I ~ 0.1-6 mA (p)
I ~ 0.03-1.5 mA (C)
High Energy
Transfer Lines
60-250 MeV p
120-400 MeV/u C
< 10^{10} p/spill (~2nA)
< 4 10^{8} C/spill (~0.4nA)
Treatment
Rooms


TERA

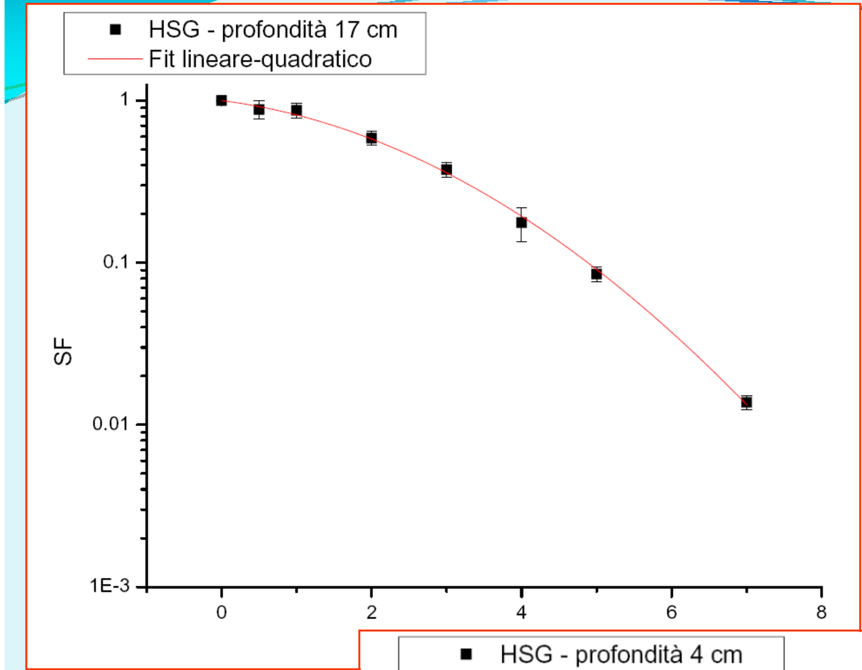
Radiobiology: cell lines irradiations

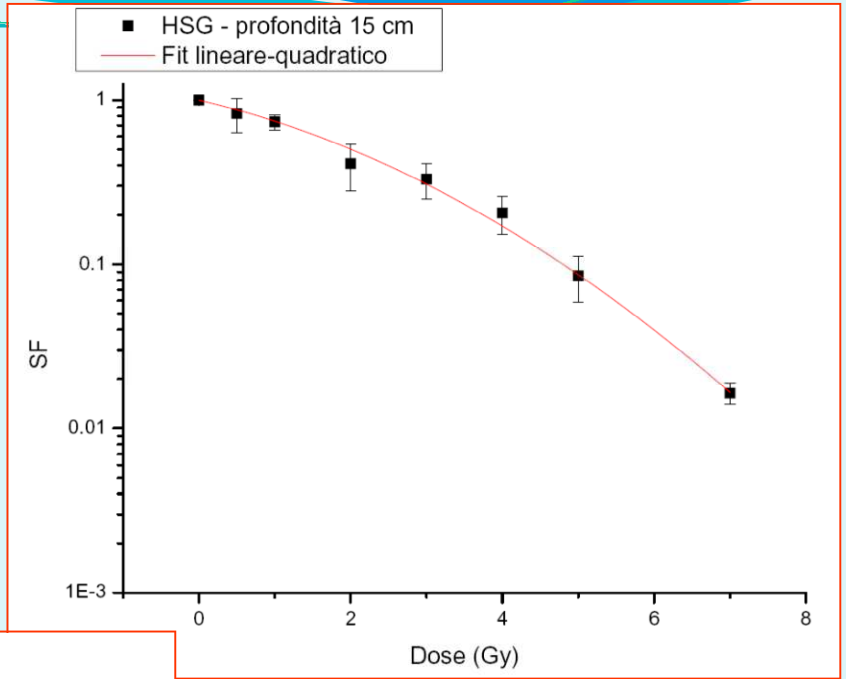


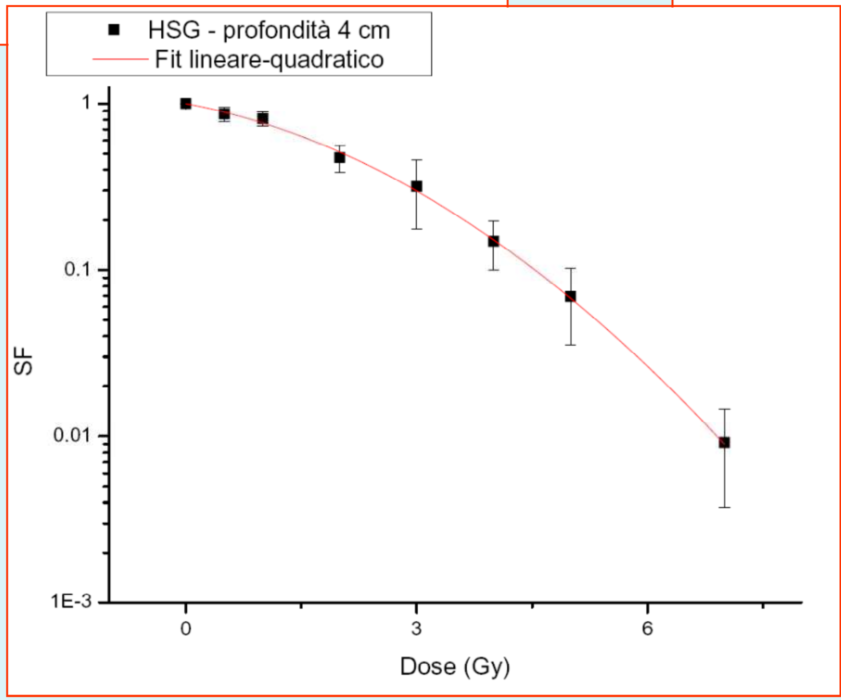
Field10x10 cm^2,
33x33 spots,
scanning step 3 mm



Survival curves – Protons: cells HSG







RBE value 1.1

CARBON IONS

Plans of 2012

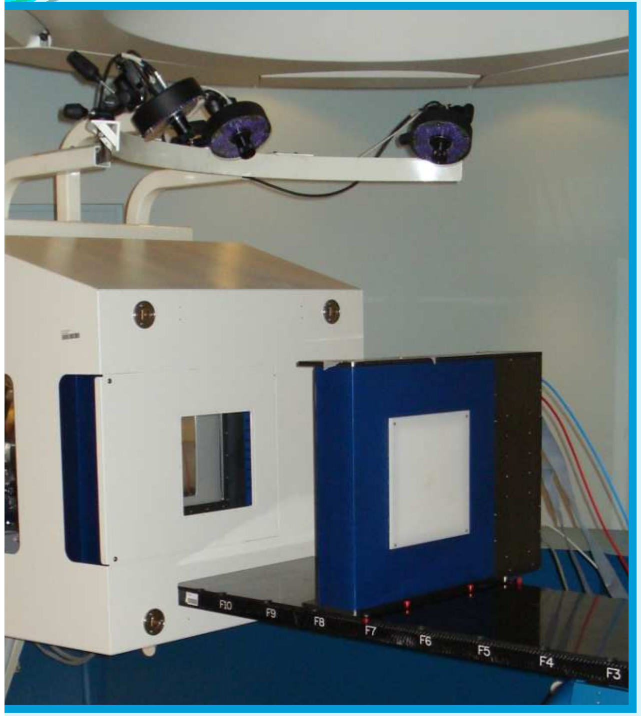
Physics and radiobiology tests within July

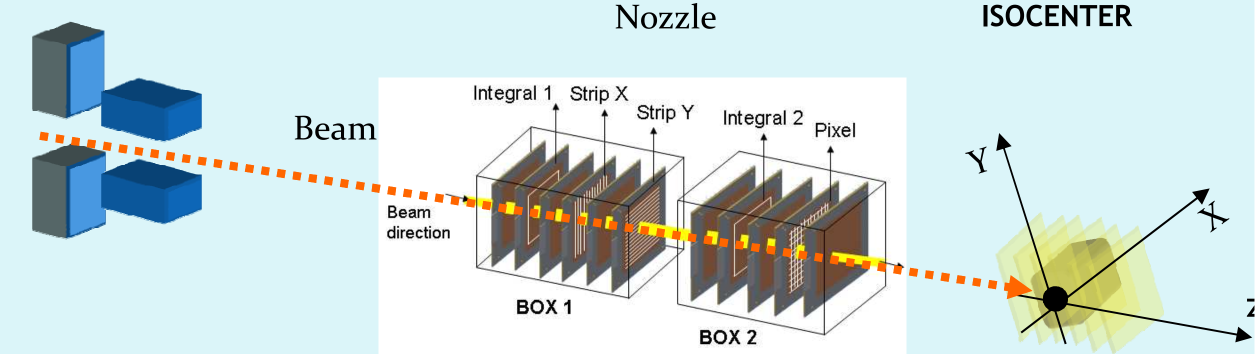
Ministry approval of treatments

Start patient treatments in Autumn

Treatments with Protons started middle of September 2011
In average 6 pts/day

Dose delivery system at CNAO





Set of parallel plate ionizationchambers

- 2 full area: *to measure the fluence (1 μs)*
- segmented in strip (along X and Y): *to measure beam position (100 μs)*
- segmented in pixel: *to measure beam dimension (50 μs)*

Scanning system

Beam is scanned on the trasverse plane by a couple of scanning magnets.
Power suppliers are controlled with optic fibers by the FPGA that handle the scanning system.
Reference current is sent every 25 µs.

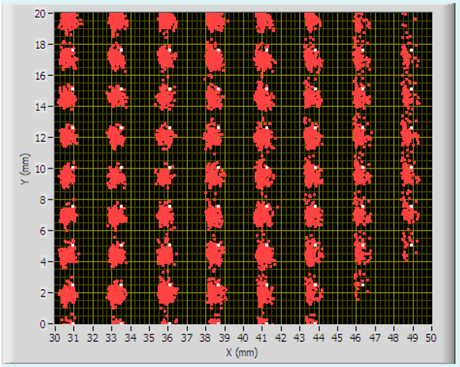
Rigidity:
- 1.14 Tm protons @ 60 MeV
- 6.38 Tm carbon ions @ 400 MeV/u

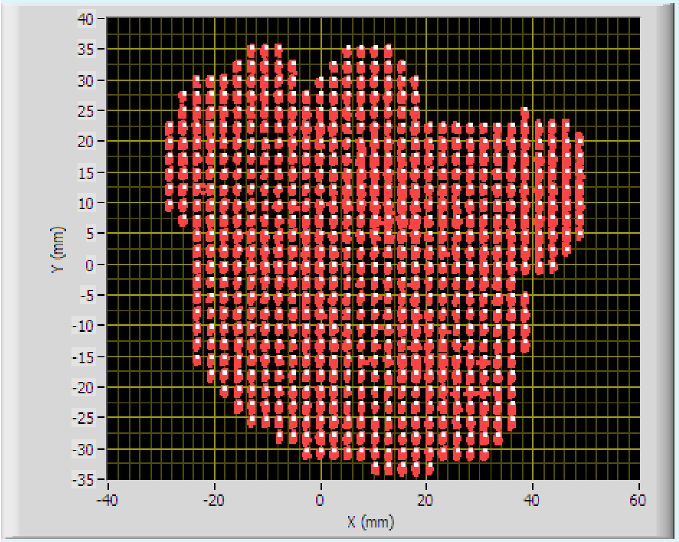
Power supply:
- Imax = 550 A
- dI/dT = 110kA/s
- ΔI > 2.5 A → ΔI/ Δt > 100 kA/sec
- ΔI < 2.5 A → time < 200 µs

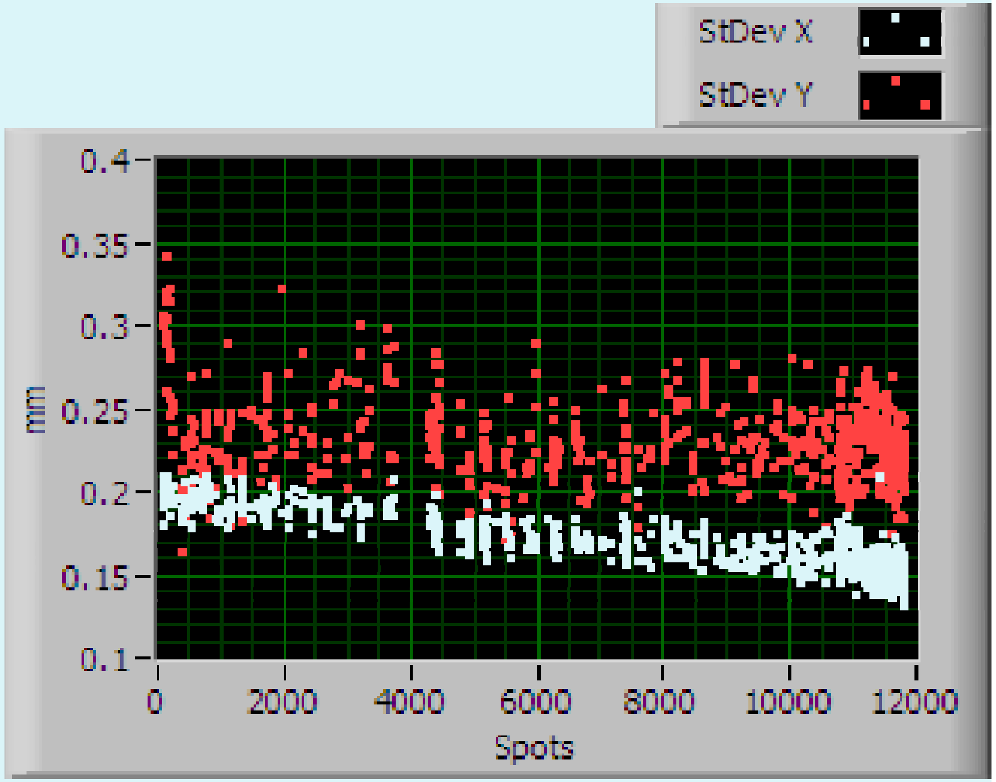
Magnet:
- isocenter distance between 4.7 m and 6.8 m
- max angle 21 mrad
- identical for x e y
- B_{max} = 0.31 T
- I_{max} = 600 A
- dB/dT = 62 T/s

Some performances of the Dose Delivery system

Comparison between measured and expected spot positions



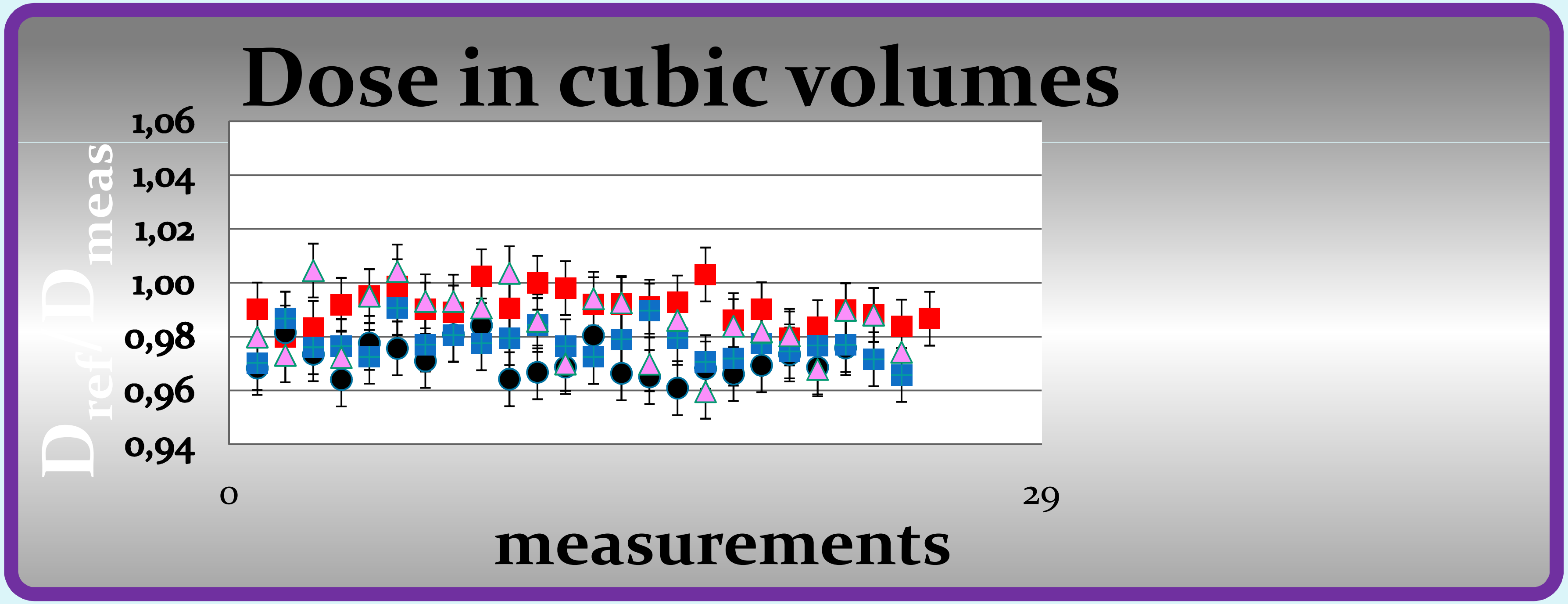




Deviation between measured and expected spot position

Control of the fluences:

for several extension of the SOBP , the ratio between reference and measured dose in different position of the volume is constant within 1%



ATreP (Trento): under construction

The clock started ticking

Dec 2, 2009: contract signature between IBA and ATreP

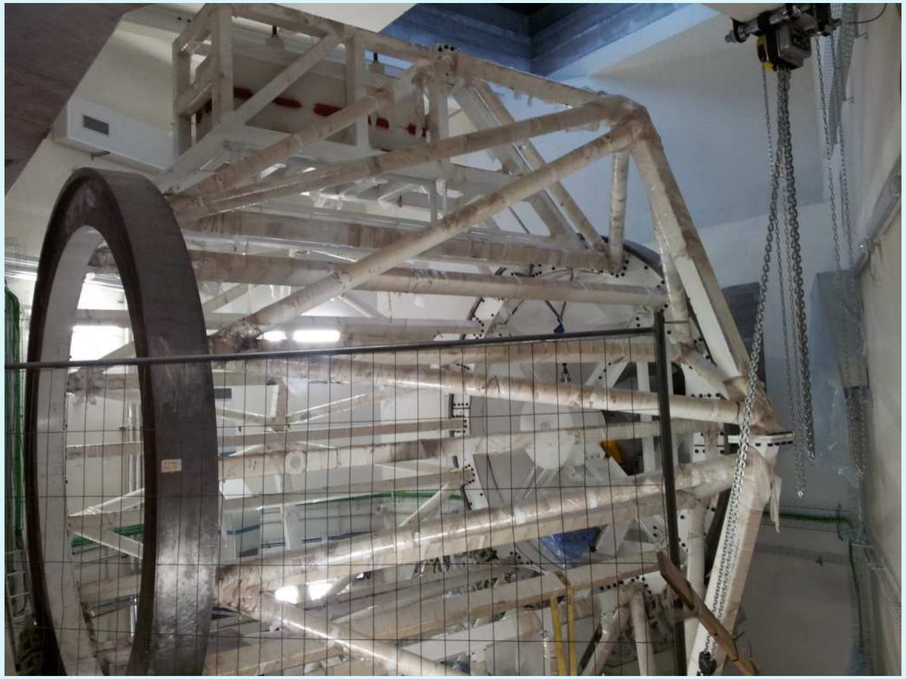
Feb 2009: option for the second gantry was exercised

Mar 2010: decision taken on companies providing imaging, ROIS, TPS and dosimetry

…

≈ May 2013: acceptance tests done on Gantry1

≈ October 2013: acceptance tests done on Gantry2



Status as of May 2012

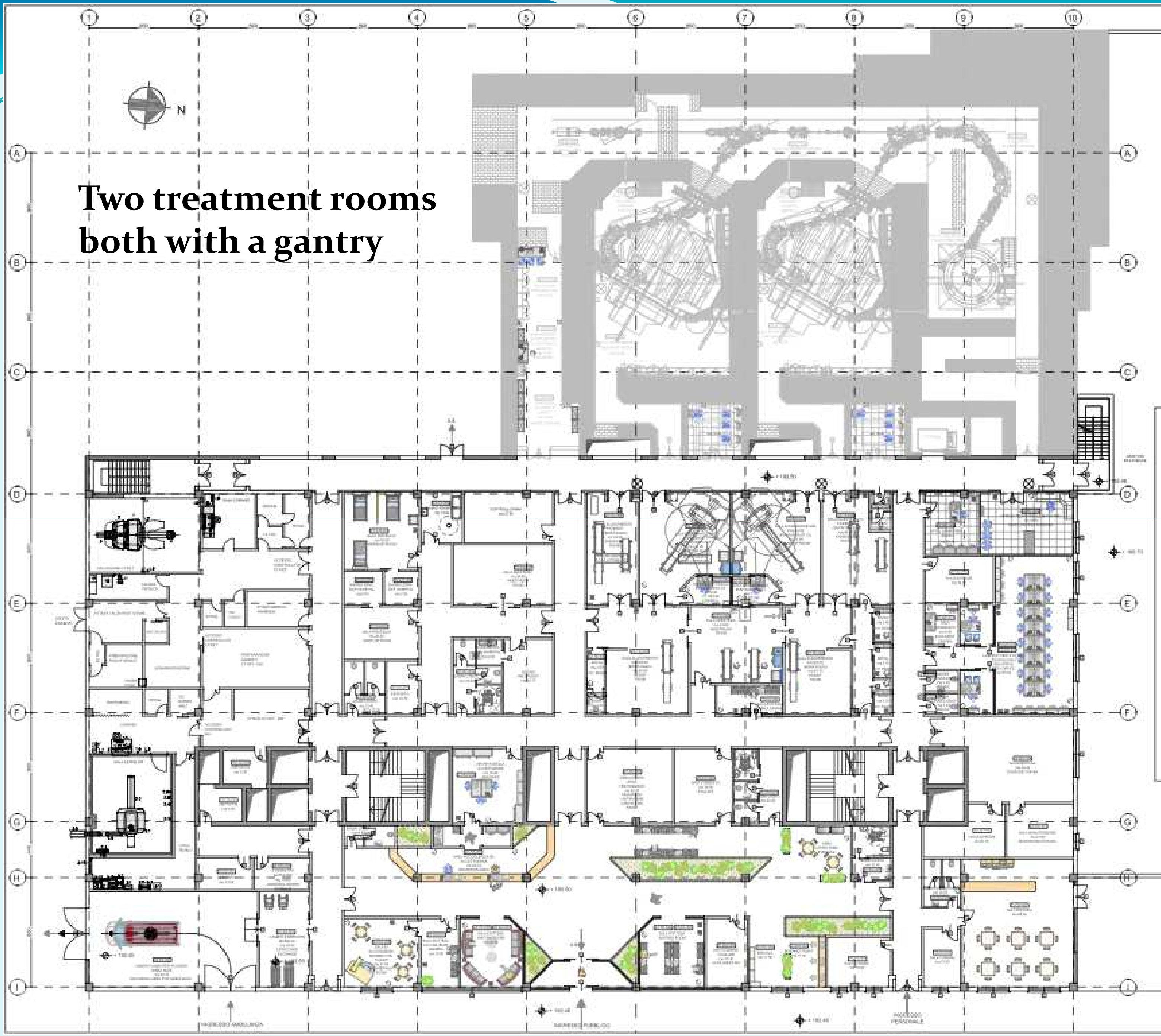
cyclotron installed

beam line installed

gantries being rigged

beam expected to be turned on at the end of the month

Two treatment rooms both with a gantry

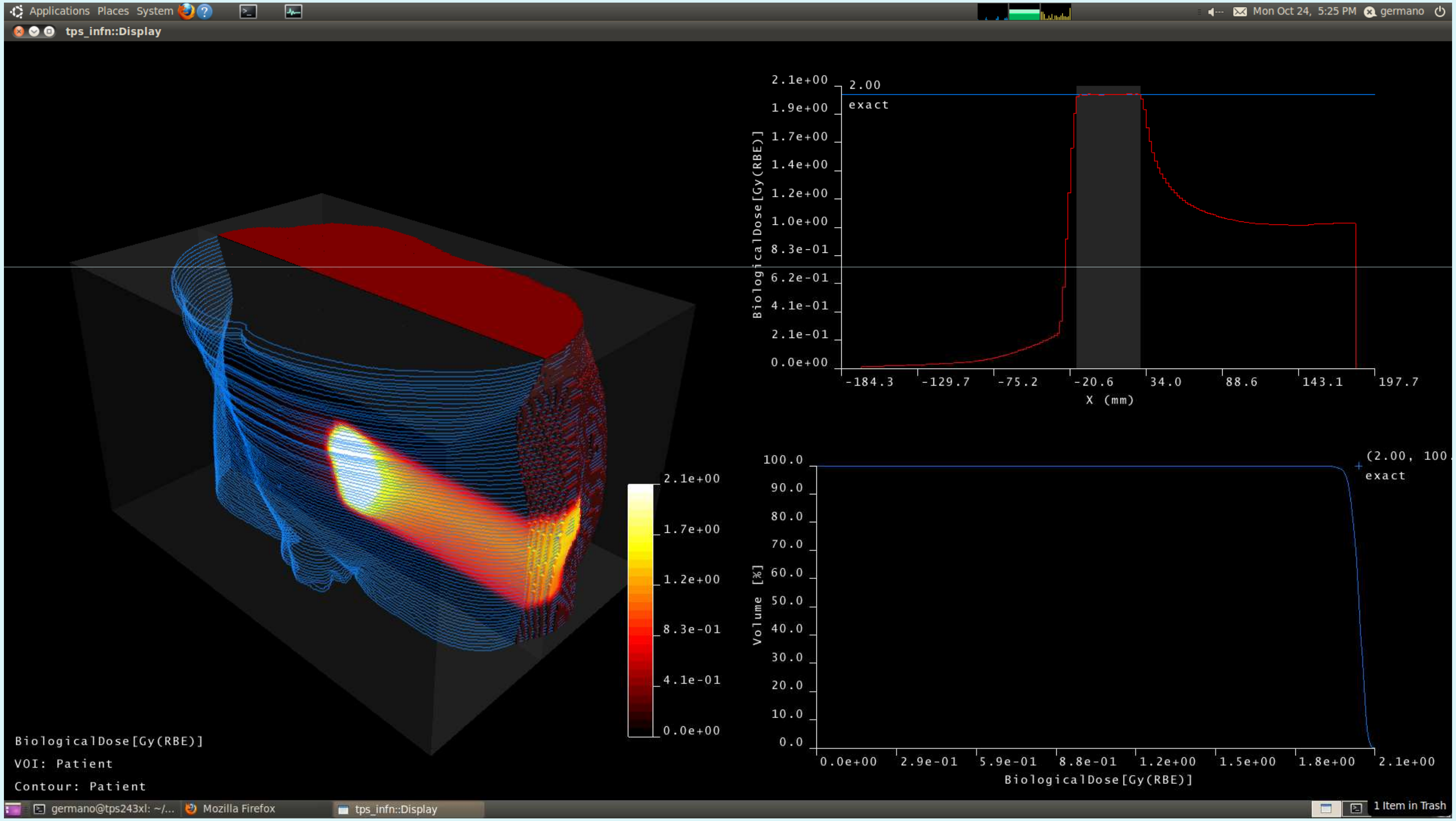


Other INFN activities: Treatment Planning System

- **INFN activity in cooperation with IBA**
- **The main purpose is to implement a Treatment Planning System for Charged Particle Therapy with active scanning dose delivery**
- **Proton and Carbon beams are included**
- **… but not only: other possible ion species are foreseen**
- **TPS activity encompasses also studies related to the Hadron therapy as:**

1. **Measurement of the fragmentation cross-sections**
2. **Radiobiology studies, both as measurements and modelization**
3. **Monte Carlo simulation**
4. **Verification of the SOBP position on the patient in real-time: *In-beam PET***

TPS: Carbon beam biological dose optimization for a prostate case for a single field



Open problems and possible future developments

NOT in order of priorities, furthermore are personal opinions

- Gantry: design, operation

- Moving organs: Treatment operations and 4D-TPS

- Is Carbon the best solution, or some other species (like Lithium) are better?

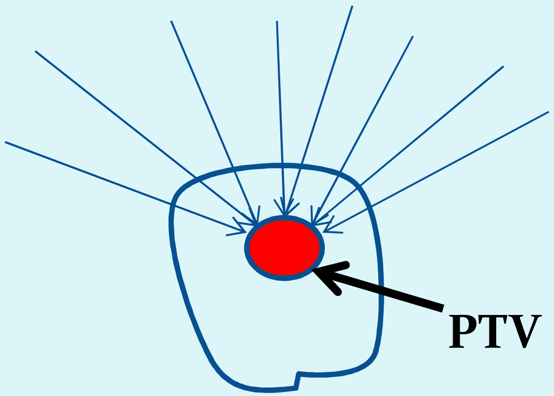
- Patient throughput (to limit the treatment cost):

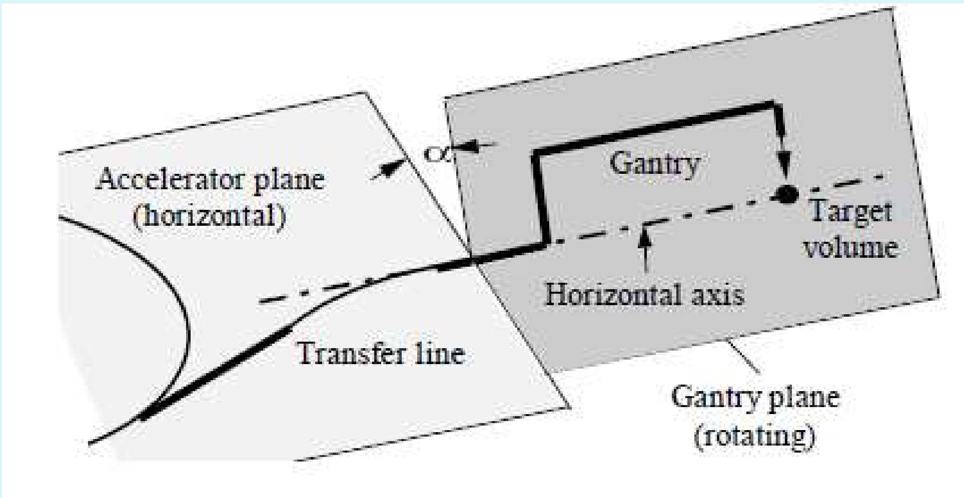
1. how to speed up the procedures?
2. ipofractionation (clinical)?

Gantry

A gantry in conventional radiotherapy

Principle of operation





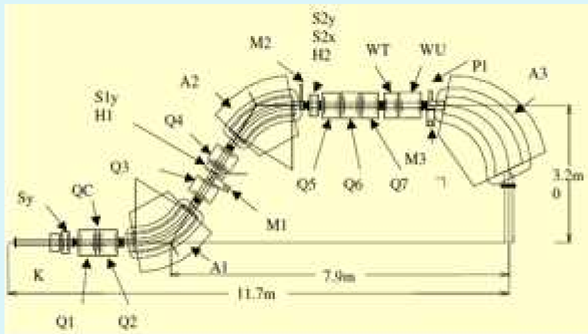
Gantry

Carbon ion gantry

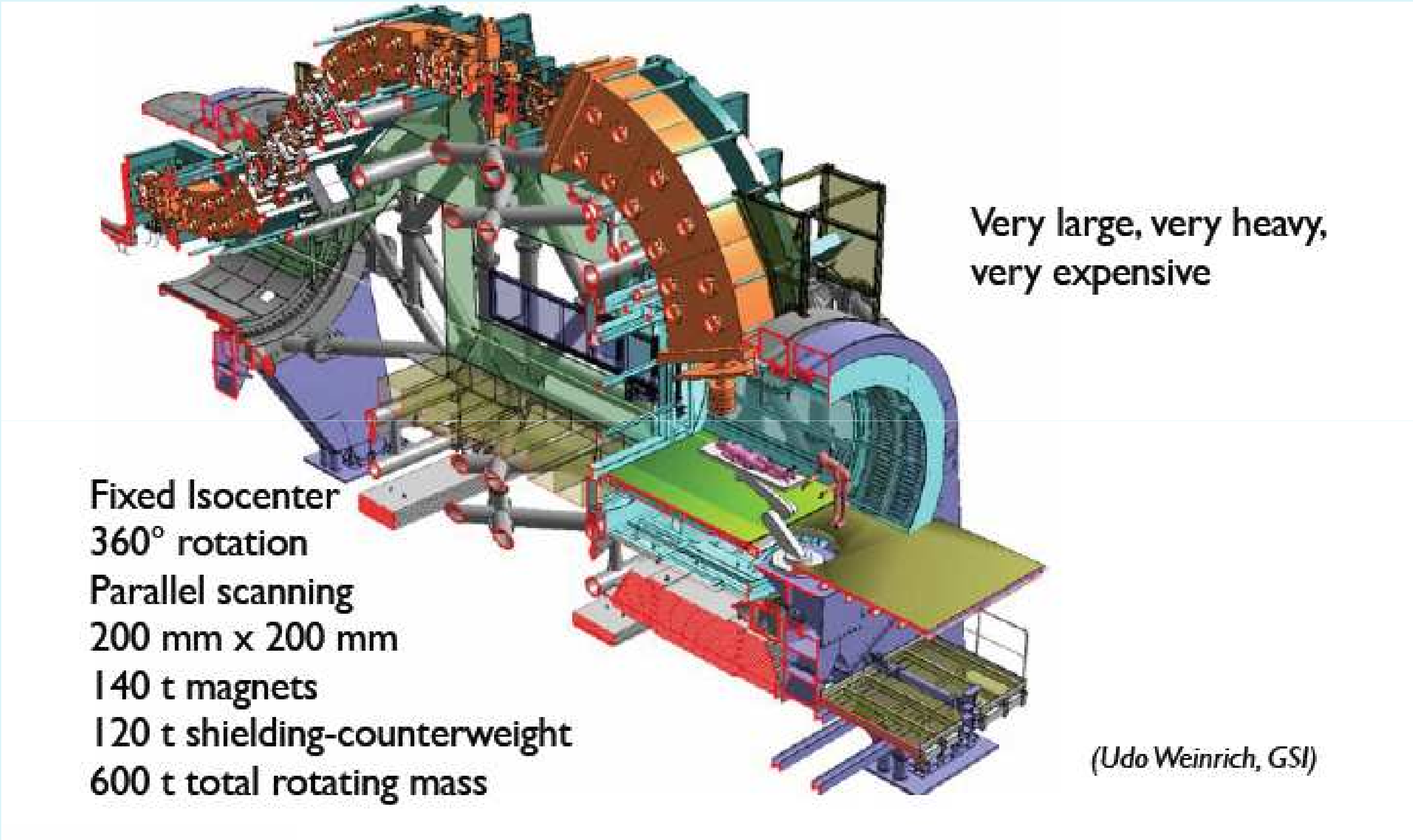
B ρ < 6.5 Tm

Proton gantry

B ρ < 2.5 Tm



Gantry for Carbon ion:
Length ~25 mt x Diameter ~13 mt -> 600 ton



Can one do it better ?
Lighter, less expensive, easy to operate?

Moving organs compensation

Due to the intrinsic precision of the dose delivery system, any movements of the tumour jeopardize the performances of the treatment

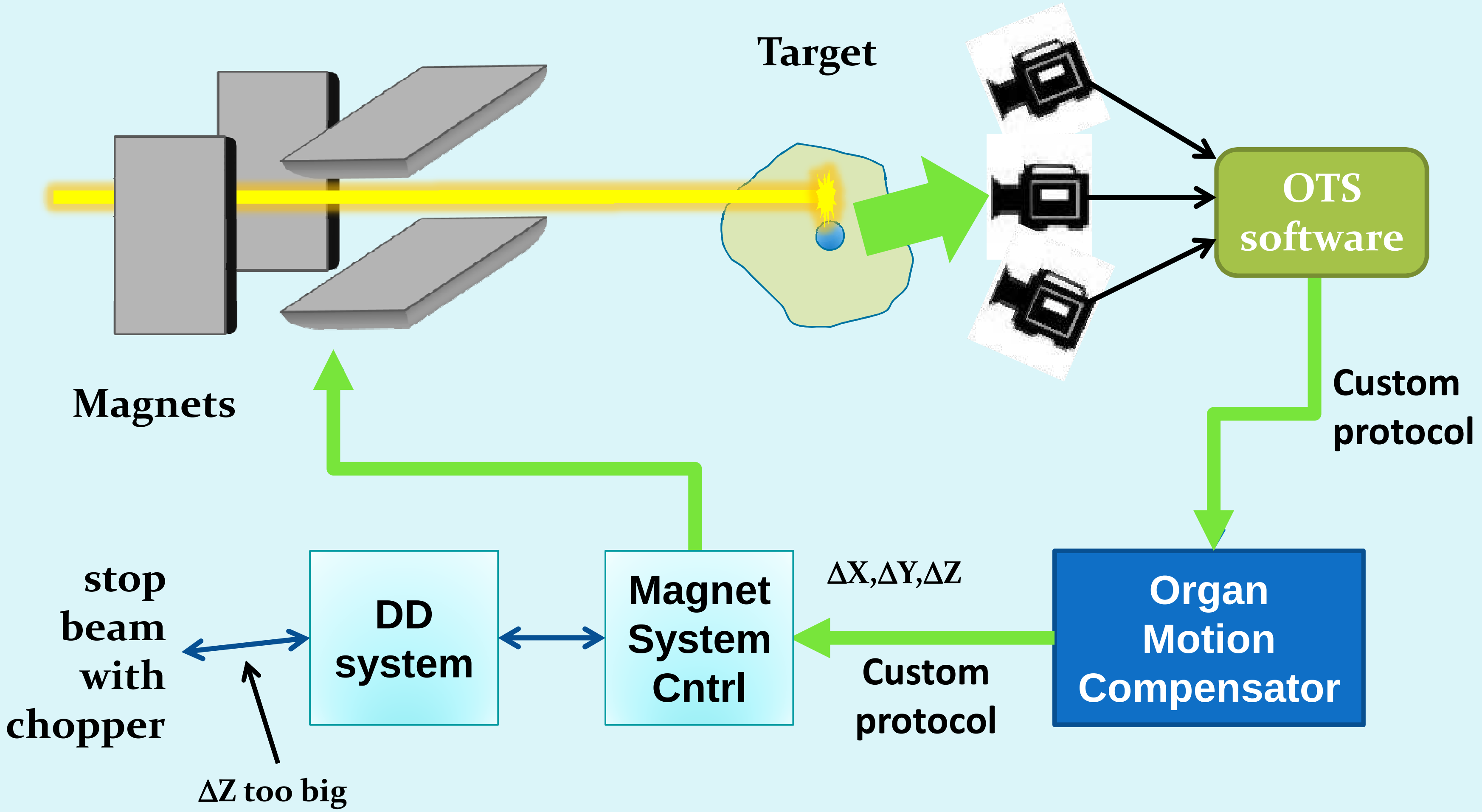
Main sources of organ motion are:

a) **Heartbeat (frequency ~1 Hz)**

b) **Respiration (frequency ~0.2÷0.3 Hz)**

Displacement: of the order of centimeters

Motion compensation strategy at CNAO



Are other particles better?

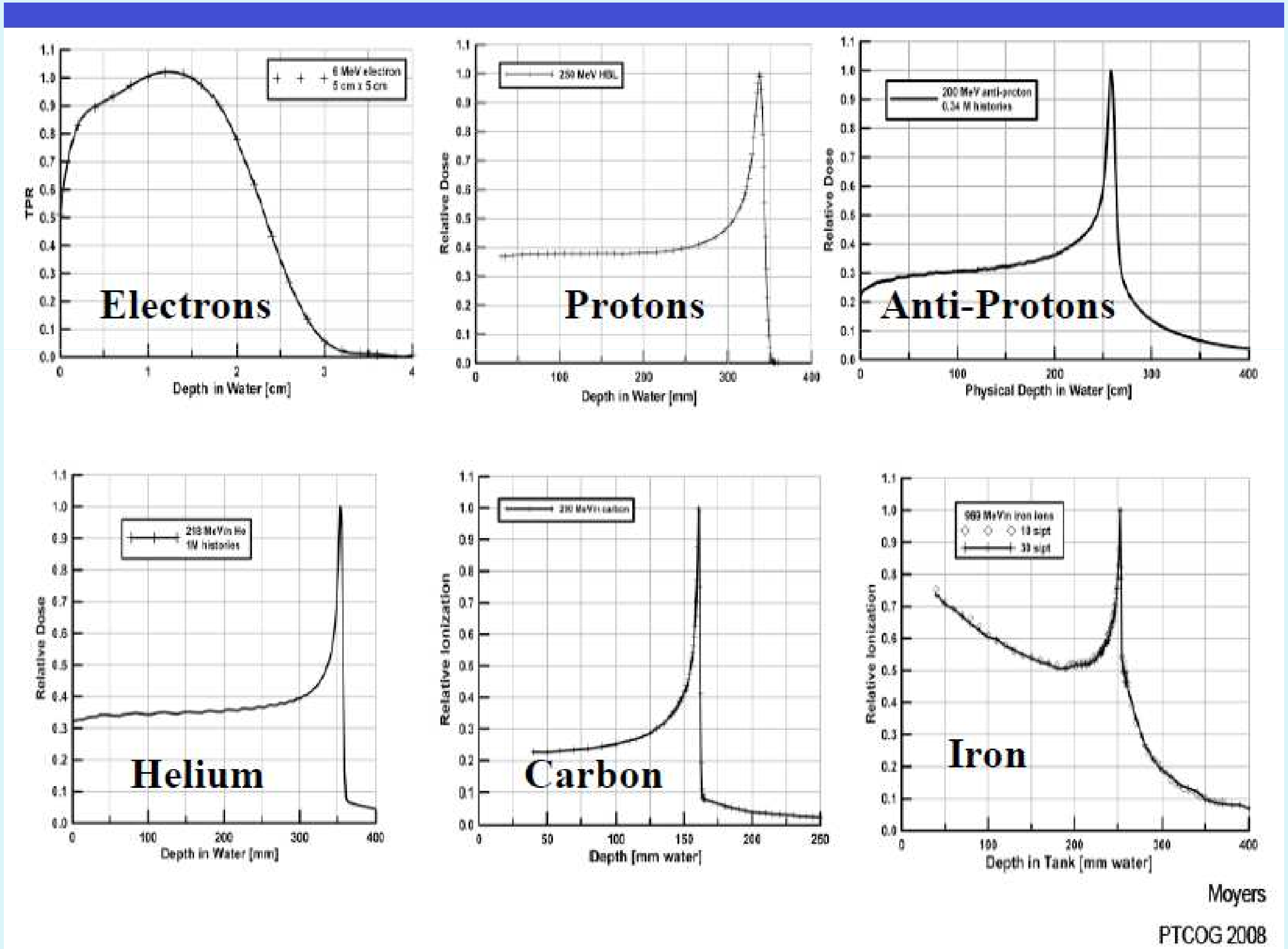


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Table 2
Properties of ions that can be accelerated by the medical synchrotron

Charged particle	E/A (MeV/A)	p (MeV/c)	p at inject. (MeV/c)	LET (eV/nm) at various residual ranges in water (cm)					Dose at R_p after 10 cm of SOBP
$^{M}N^{Z}$	Range 26.2 cm	Range 26.2 cm	$E = 7$ MeV/u	26.2	15	7	3	0.1	(% dose)
e^{-a}	56.0	56.0	–	0.2	0.2	0.2	0.2	0.2	5.5
~~$^{1}H^{+1}$~~	*200.0*	645	115	0.5	0.6	0.8	1.1	4.9	1.5
~~$^{2}D^{+1}$~~	136.0	1045	160	0.6	0.7	1.0	1.5	6.9	2.5
~~$^{3}T^{+1}$~~	108.0	1385	345	0.7	0.9	1.2	1.8	8.3	3.0
~~$^{3}He^{+2}$~~	238.5	2125	345	1.6	2.0	2.7	3.9	17.8	3.5
~~$^{4}He^{+2}$~~	202.0	2580	457	1.8	2.2	3.1	4.4	19.6	4.0[b]
$^{7}Li^{+3}$	234.1	4905	800	3.7	4.6	6.2	8.9	41.0	7.0
$^{9}Be^{+4}$	283.7	7050	1035	5.9	7.2	9.6	13.7	62.4	12.0
$^{11}B^{+5}$	329.5	9350	1260	8.5	10.2	13.6	19.3	87.7	17.0
$^{12}C^{+6}$	391.0	11260	1370	11.1	13.4	17.7	24.7	111.8	22.0[b]
~~$^{14}N^{+7}$~~	430.5	13910	1600	14.5	17.3	22.6	31.6	142.2	28.0
~~$^{16}O^{+8}$~~	468.6	16710	1830	18.2	21.6	28.1	39.2	175.1	35.0
~~$^{20}Ne^{+10}$~~	540.8	22847	2297	26.8	31.5	40.6	55.9	248.7	51.0[b]

40 eV/ 2 nm (DNA) ->20 eV/nm

Thank you