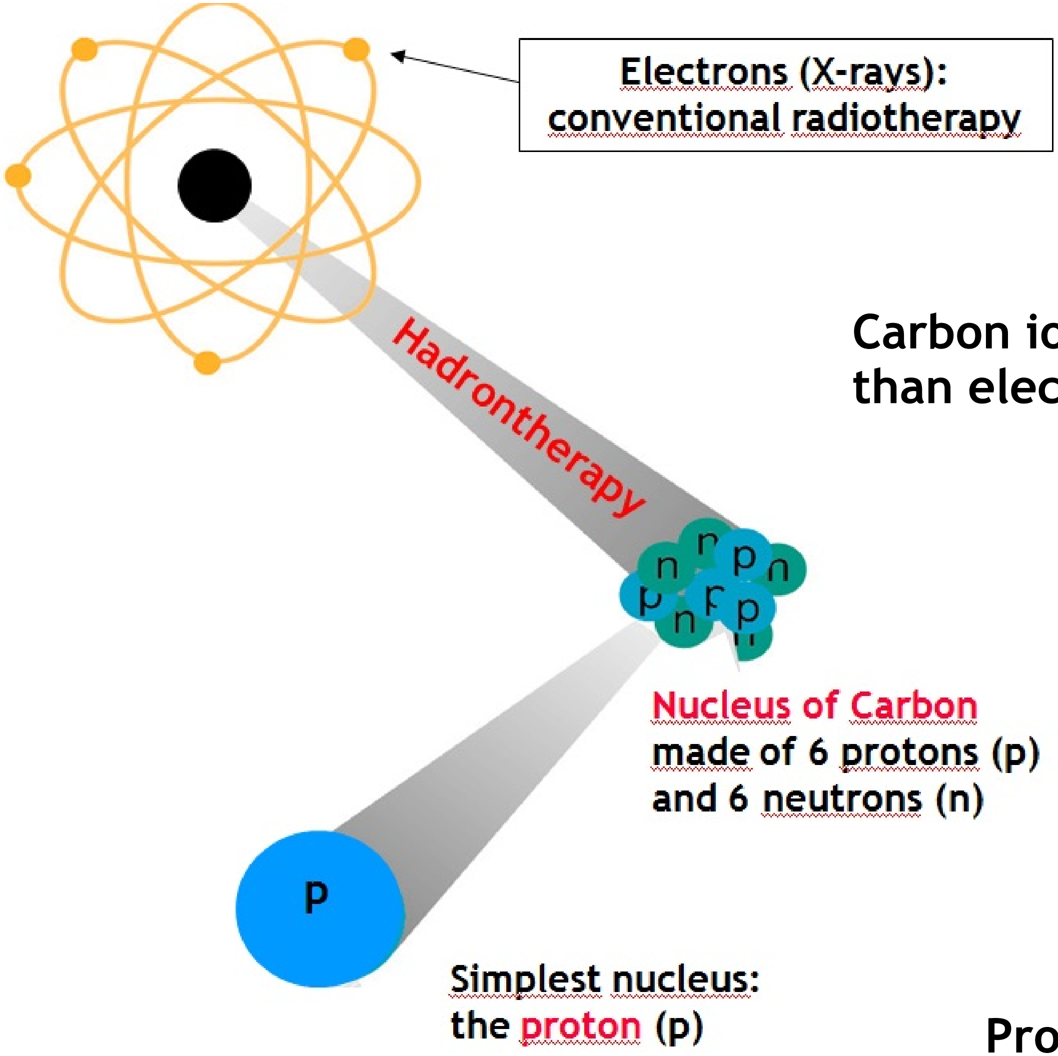
Hadrontherapy: a new energy against tumors

Mutti Viviana – CNAO Foundation

INFN – LNF – February 16th, 2018

fondazione CNAO
Centro Nazionale di Adroterapia Oncologica

Hadrontherapy ?



Carbon ion is 12x2000 times heavier than electron

Proton is 2000 times heavier than electron

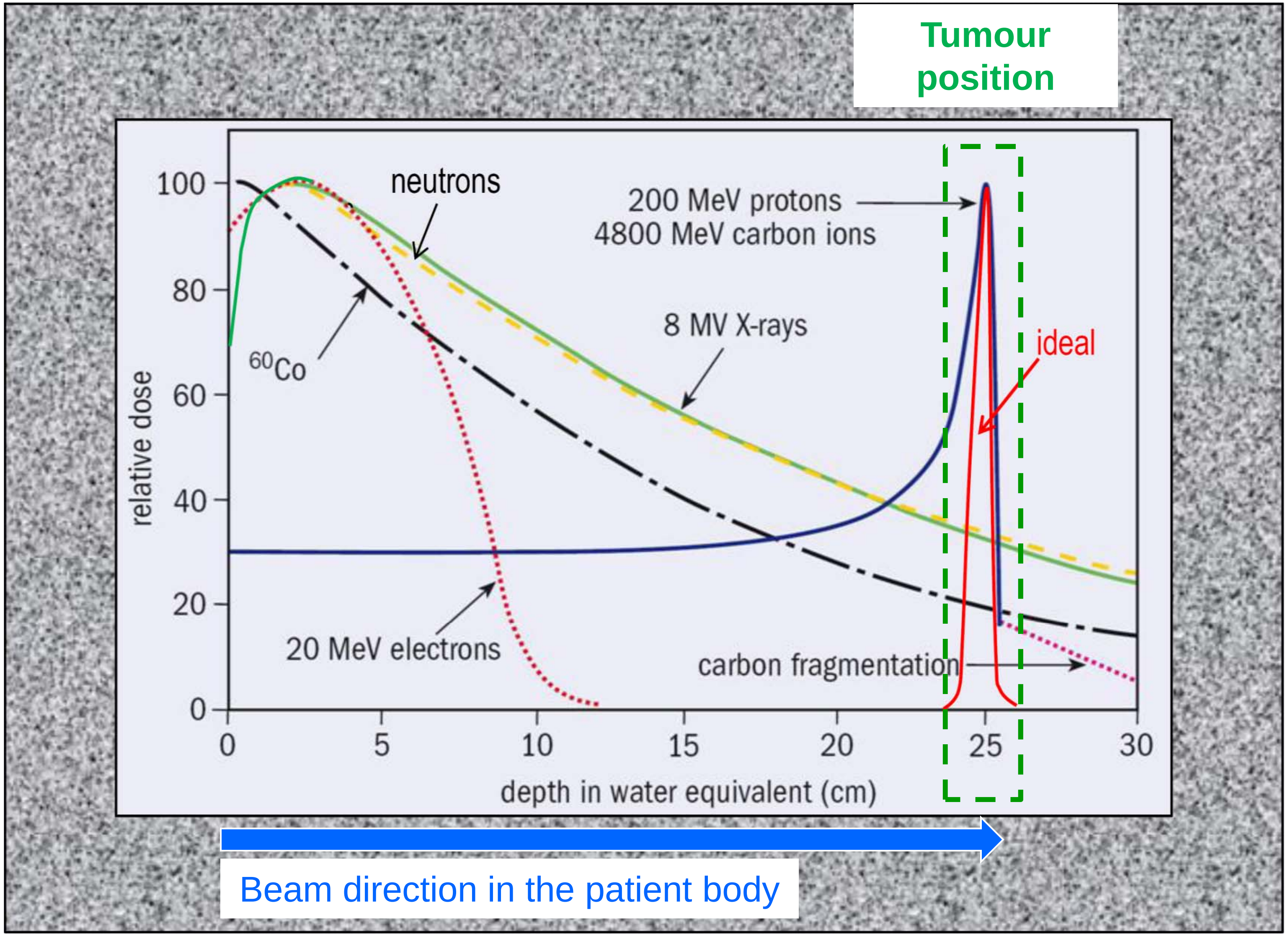
Which advantages with hadrons ?

+ PRECISION

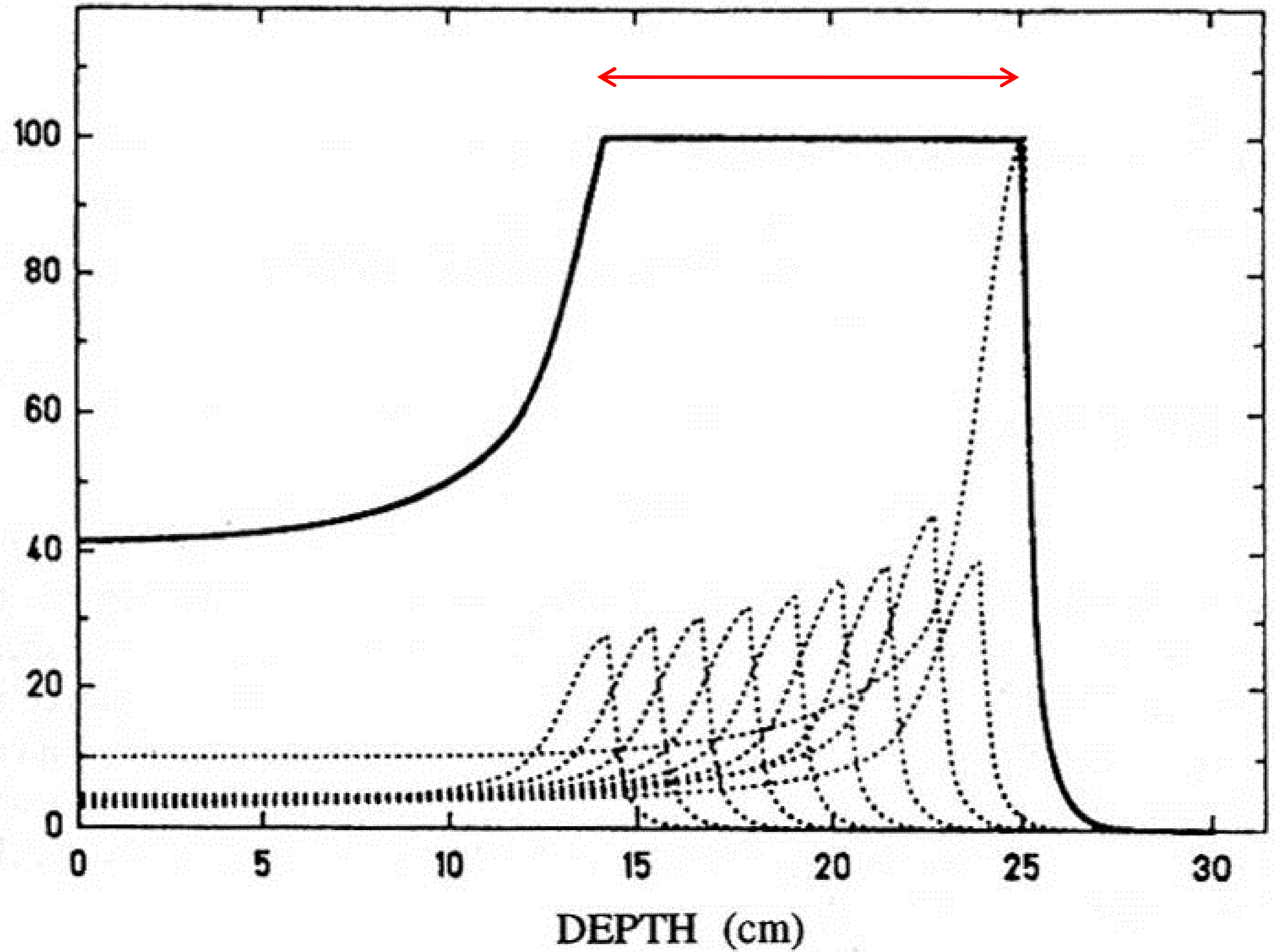
↓

Conformal irradiation of tumour volume
(= reduced damages to healthy tissues)

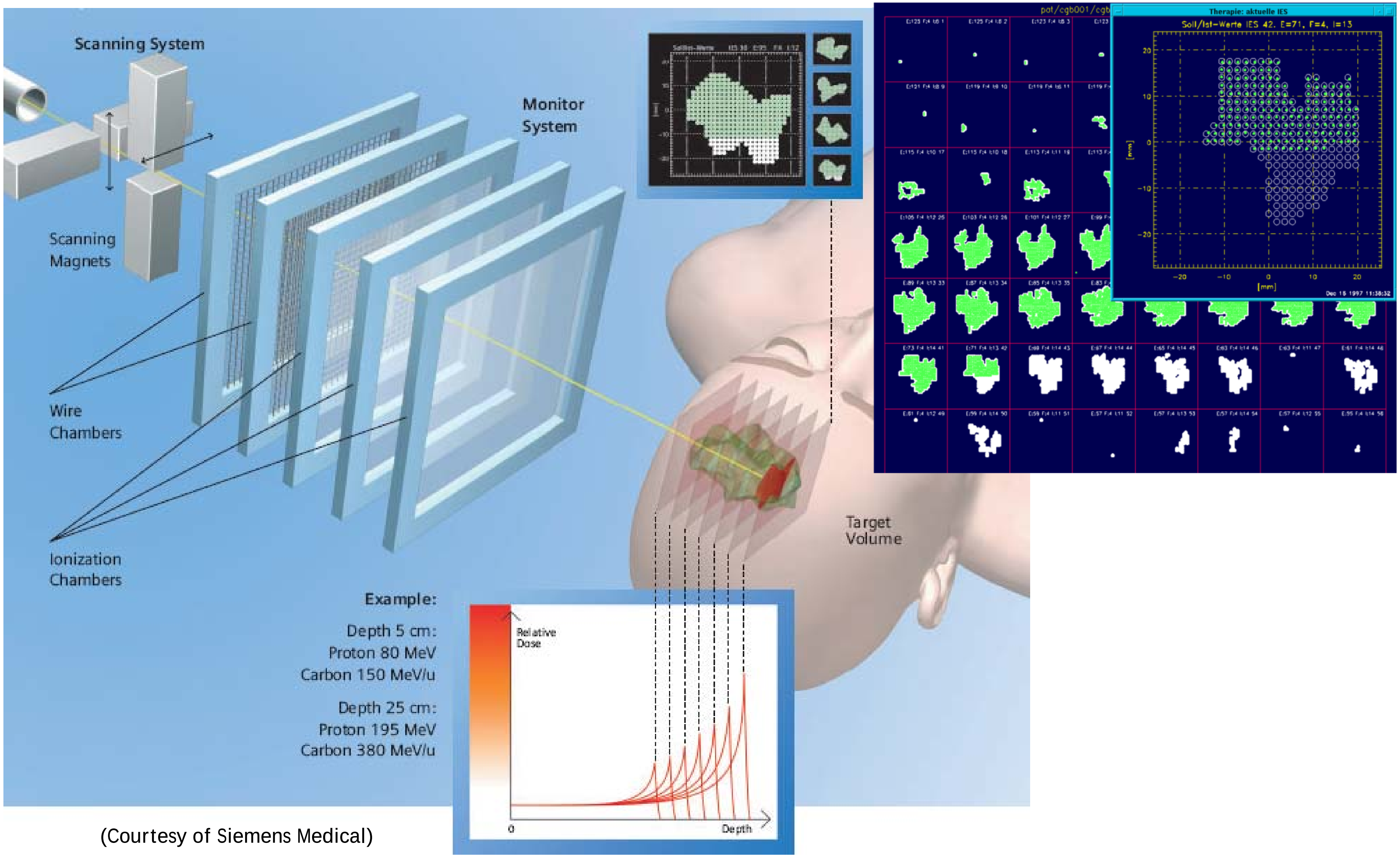
Precision in hadrontherapy



Precision in hadrontherapy



Irradiation technique active scanning

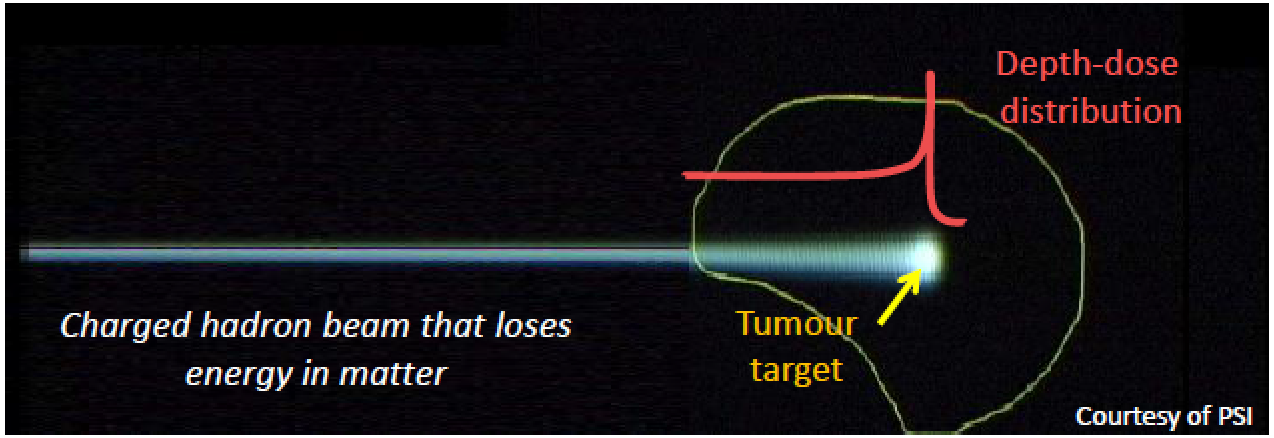


(Courtesy of Siemens Medical)

Hadron beams in matter

200 MeV - 1 nA
protons

400 MeV/u – 0.1 nA
carbon ions
(radioresistant tumours)



• While passing through matter, a hadron loses most of its energy when it is almost stopped, at the so-called *Bragg peak.*

• High doses can be delivered to tumour target while providing low doses to frontal and distal healthy tissue.

• The position of the Bragg peak depends on the energy of the hadron at the volume entrance.

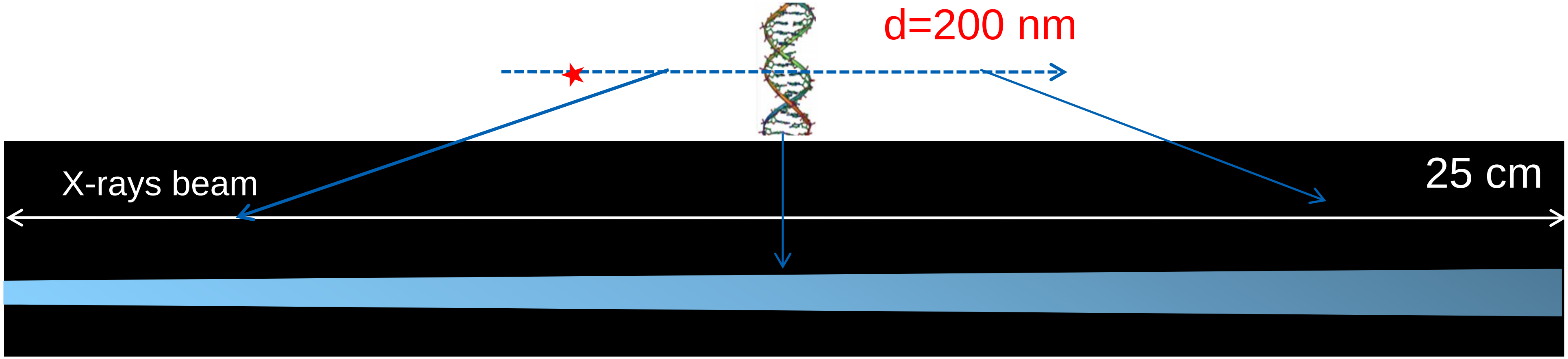
Which advantages with hadrons ?

+ EFFICACY

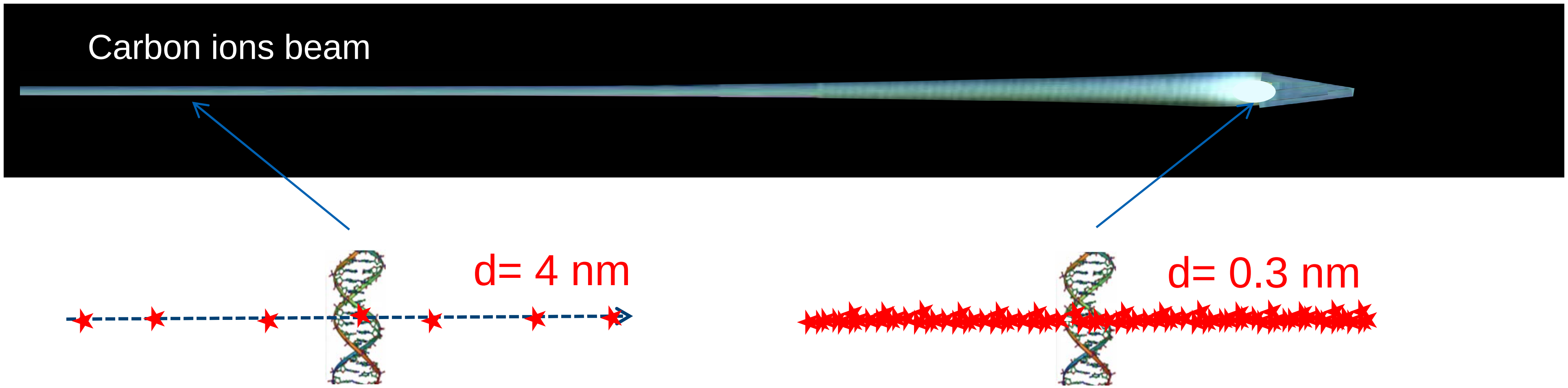
↓

Increased radiobiological efficacy of carbon ions
(= DNA of tumour cells destroyed in multiple hits)

X-rays: sparse damage and indirect effects



Carbon ions: clustered damage on tumour and direct effect



Number of potential patients

European Country: 60 MILLIONS HABITANTS

X-Ray therapy (photons 5 – 20 MeV)

New patients per year: 150'000 pts/y

Protons

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

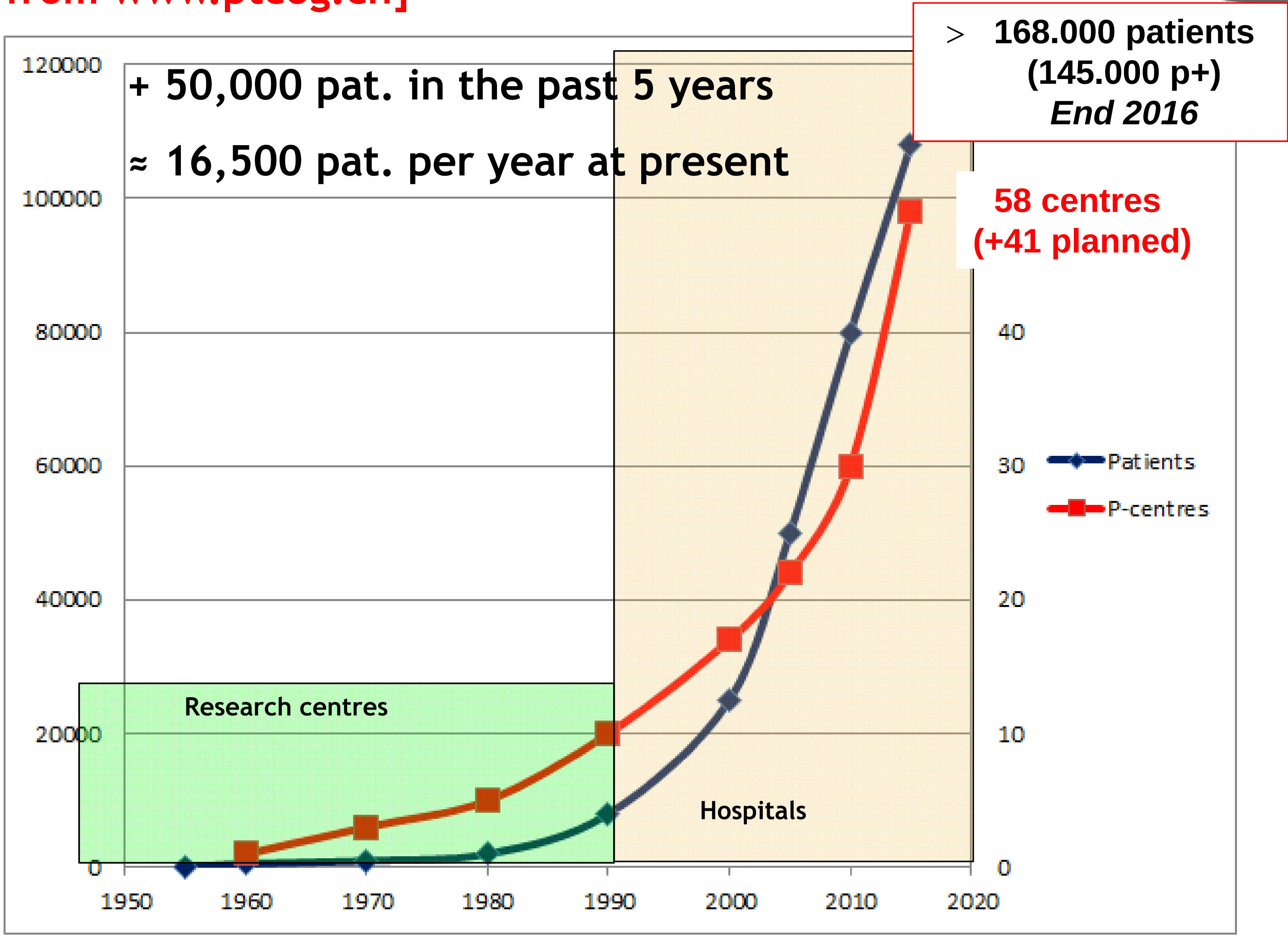
Category B: good indications = 12'000 pts/y

Carbon ions

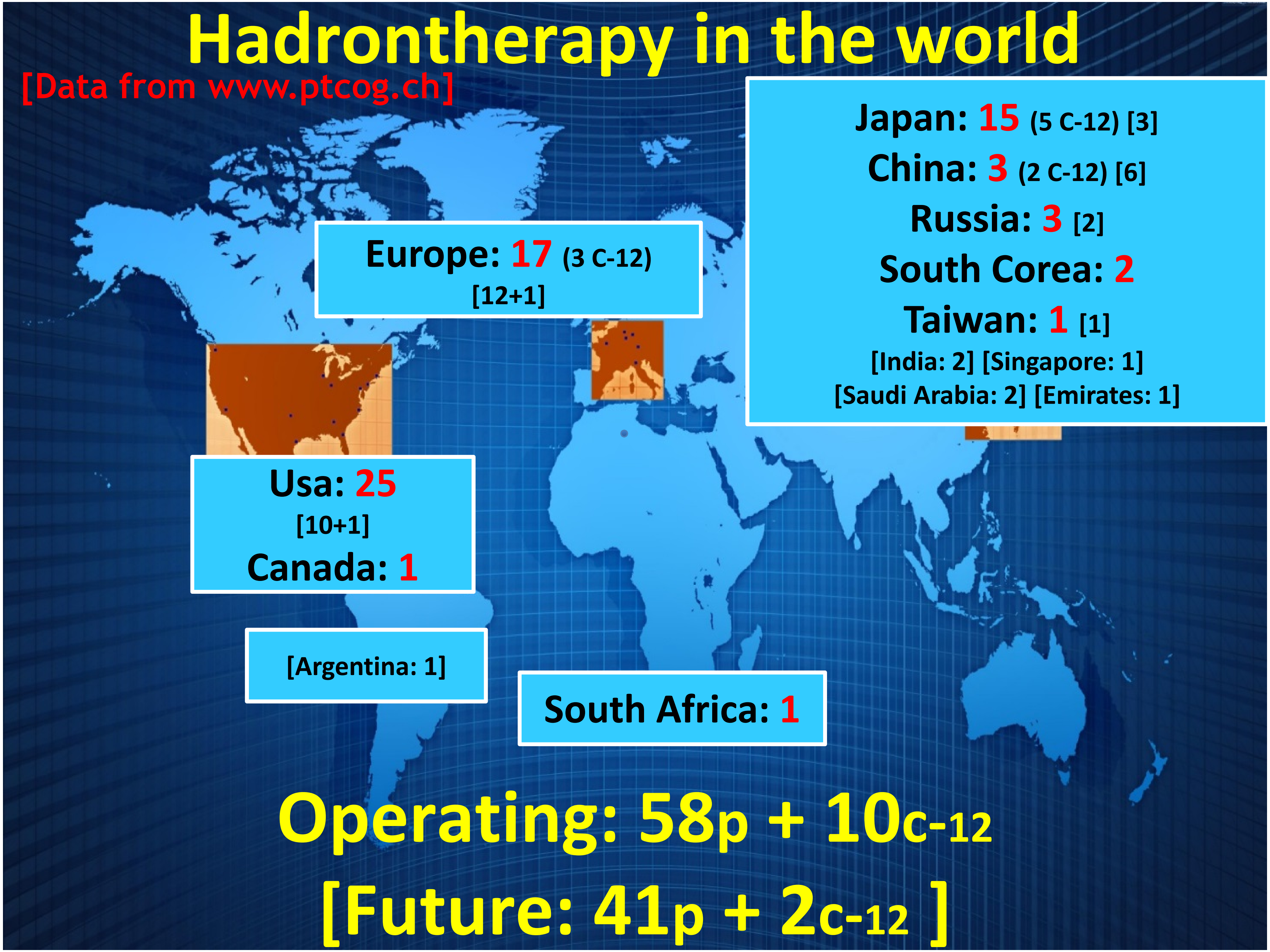
% radioresistant tumours 1'500 pts/y

IDEAL → **1 dual centre (p and C)**
Possibly 1 protontherapy centre every 10 M citizens

[Data from www.ptcog.ch]



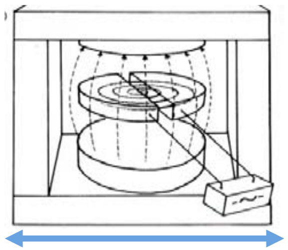
Carbon Ions: > 23.000 patients; 10 centres (5 multi ions+2 in construction)


Hadrontherapy in the world
[Data from www.ptcog.ch]
Japan: 15 (5 C-12) [3]
China: 3 (2 C-12) [6]
Russia: 3 [2]
South Corea: 2
Taiwan: 1 [1]
[India: 2] [Singapore: 1]
[Saudi Arabia: 2] [Emirates: 1]
Europe: 17 (3 C-12)
[12+1]
Usa: 25
[10+1]
Canada: 1
[Argentina: 1]
South Africa: 1
Operating: 58p + 10C-12
[Future: 41p + 2C-12]

The accelerators used today in hadrontherapy are "circular"

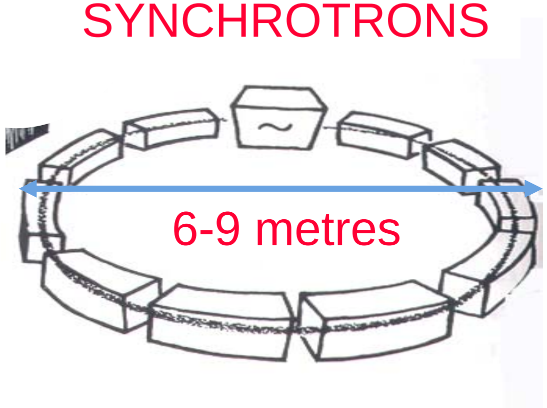
Teletherapy with protons (200-250 MeV)

CYCLOTRONS (*) (Normal or SC)



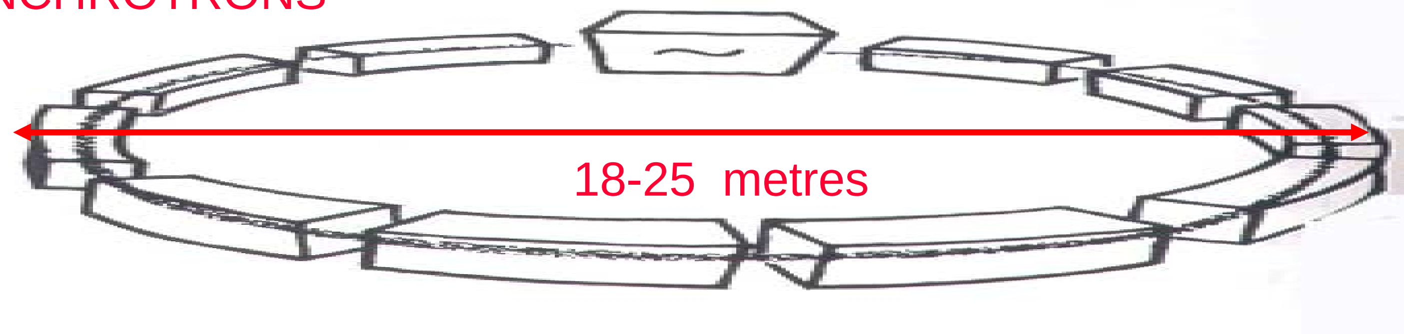
(*) also synchrocyclotrons

SYNCHROTRONS



Teletherapy with carbon ions (4800 MeV = 400 MeV/u)

SYNCHROTRONS



Cyclotron

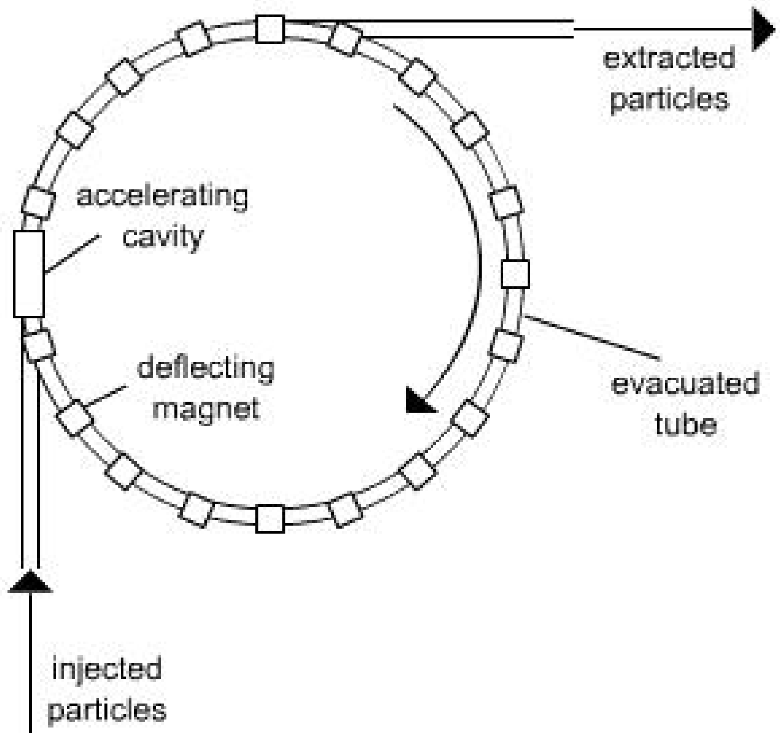
Spiral trajectory

B = constant

Dynamic law: $\omega_{rev} = \frac{qB}{m}$

Fixed frequency, high intensities

Synchrotron



Circular trajectory

ρ = constant

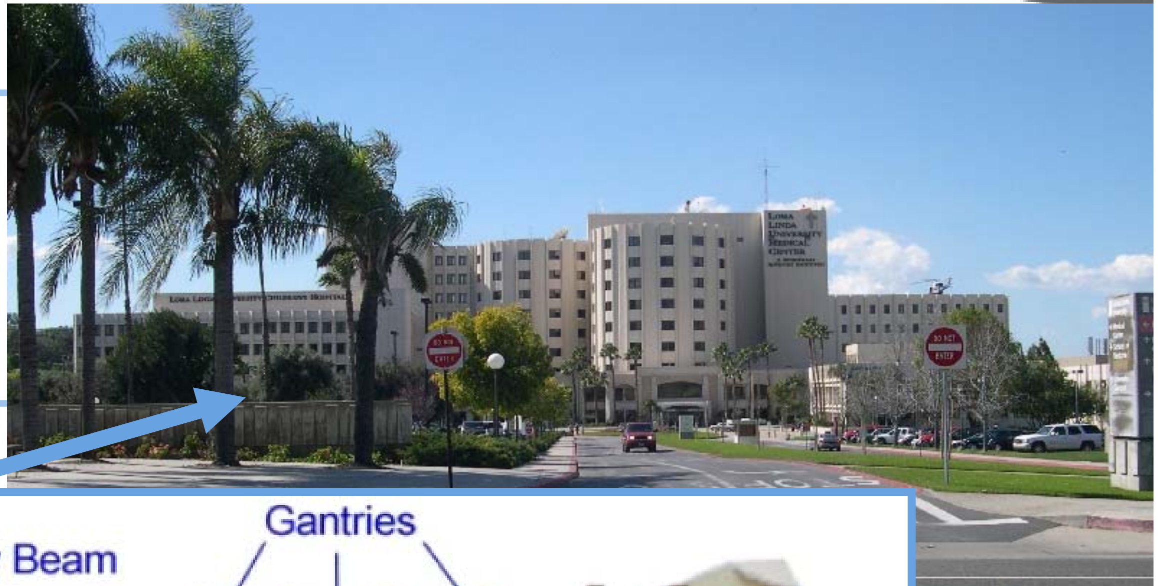
Dynamic law: $p = qB\rho$

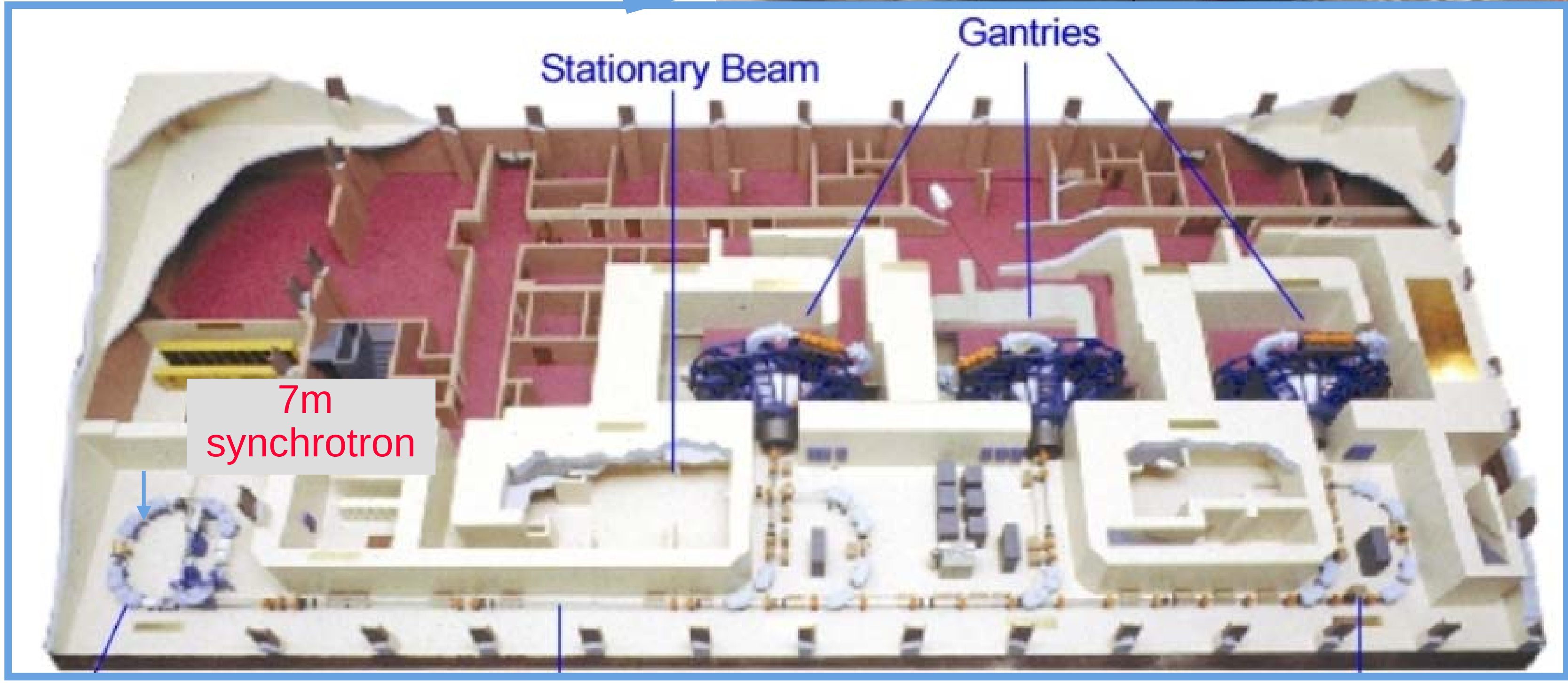
Energy increases with B

Loma Linda University Medical Center: first patient 1992

First hospital based protontherapy centre (1992)

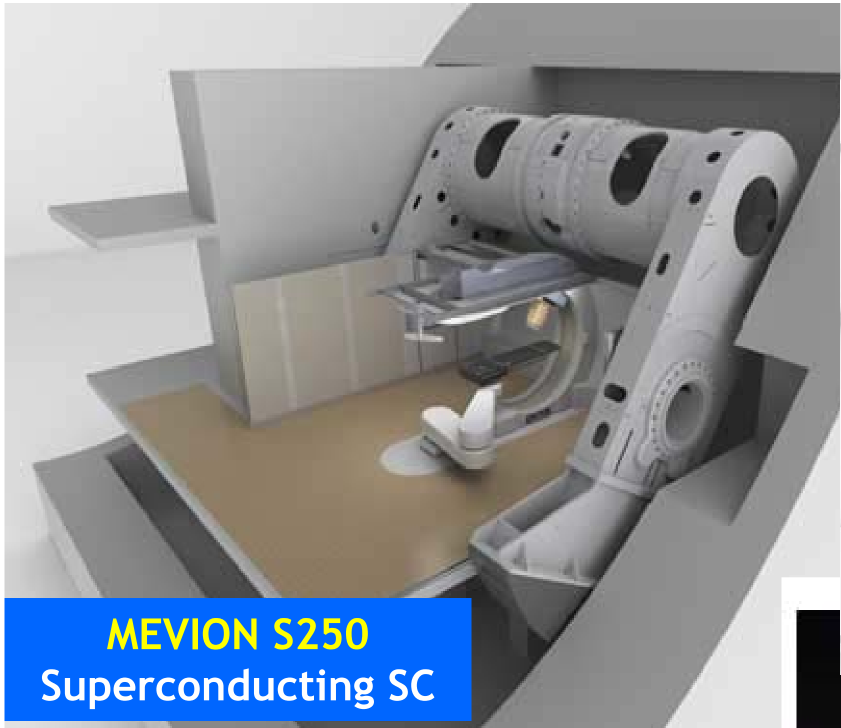
2012:160 sessions/d





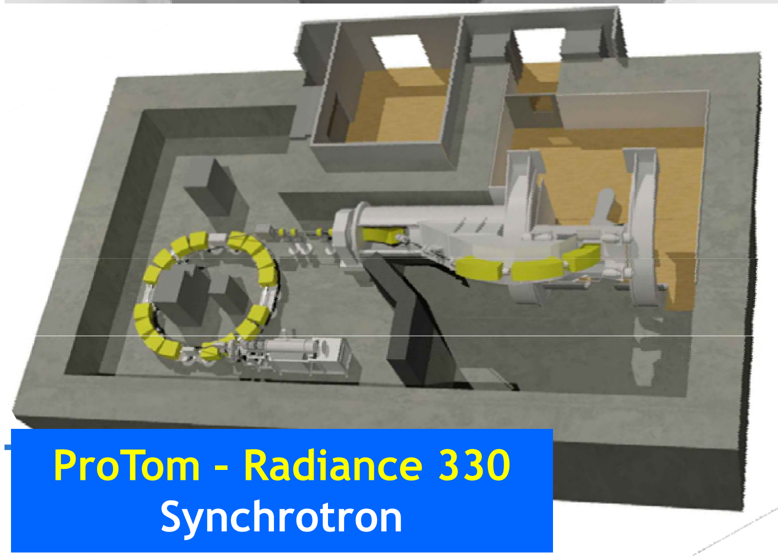
Optivus Ltd. commercialises this centre

Single room facilities for protontherapy

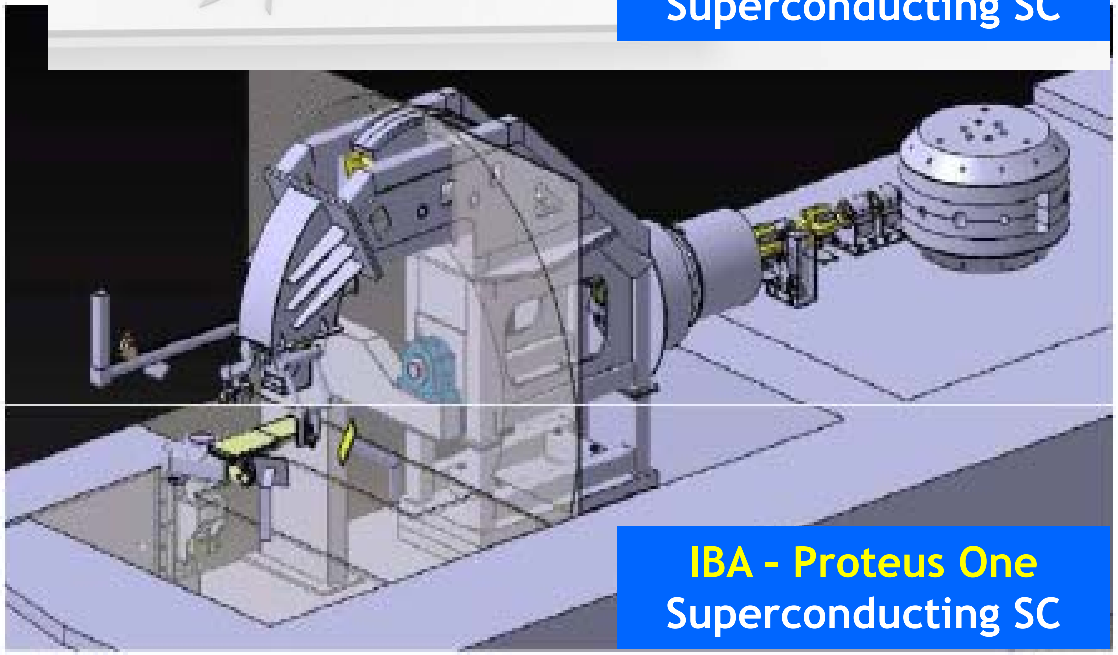


MEVION S250
Superconducting SC

Varian - Probeam
Superconducting SC



ProTom - Radiance 330
Synchrotron



IBA - Proteus One
Superconducting SC

HIMAC

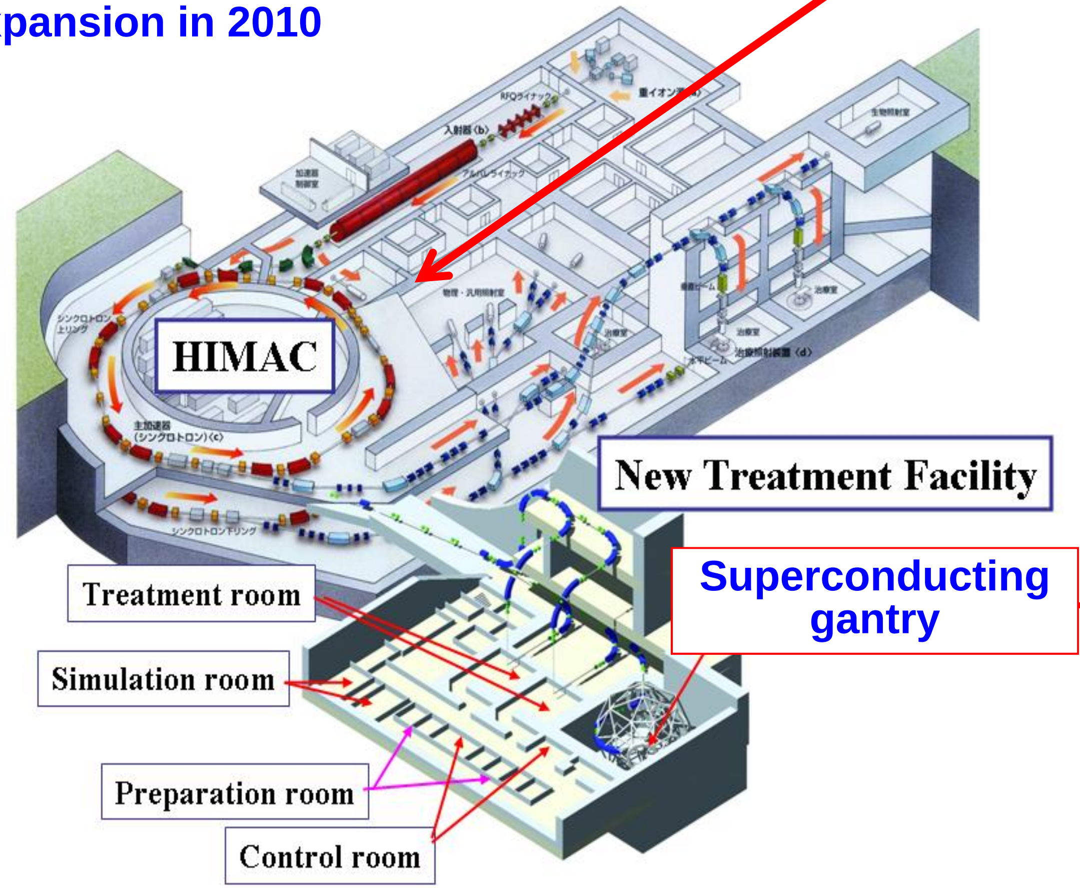
Heavy Ion Medical Accelerator in Chiba

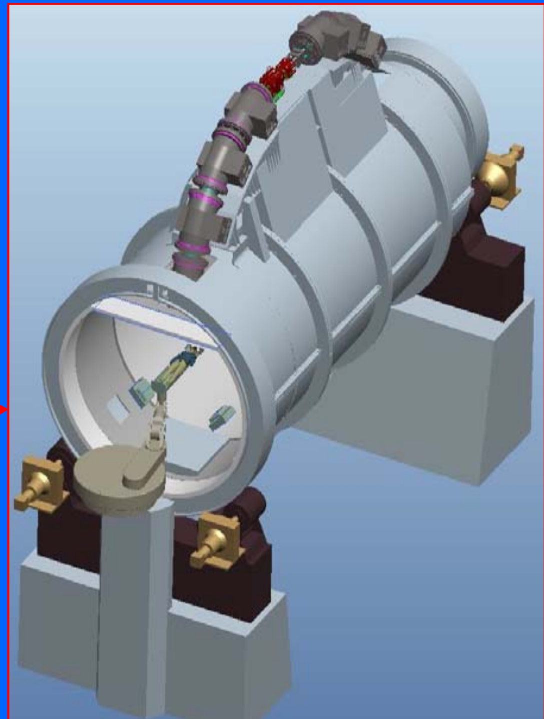
(First patient in 1995)

Carbon Ion facilities

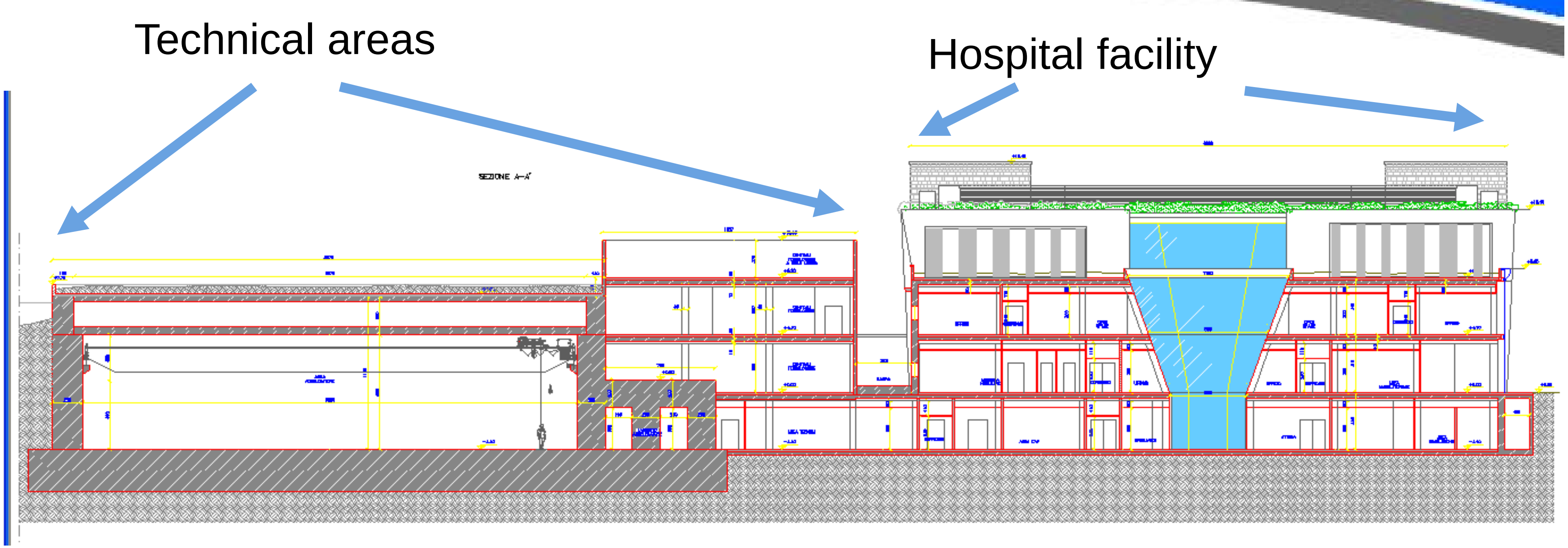
2 synchrotrons 800 MeV/u, therapy and nuclear physics

Expansion in 2010






CNAO – Pavia



HOSPITAL FACILITY DEVELOPING ON FOUR LEVELS

Surface Level (L.0): reception, first visit, follow up visits and medical imaging

Underground level (L. -1): treatment area

First floor (L. 1): administration, offices and laboratories

Second floor (L. 2): direction, conference and meeting rooms

CERN/PPE/UA/eo

25 Maggio 1991

Per un Centro di Teleterapia con Adroni

Ugo Amaldi

CERN e Università di Milano

Giampiero Tosi

Ospedale di Niguarda, Servizio di Fisica Sanitaria,
e Università di Milano

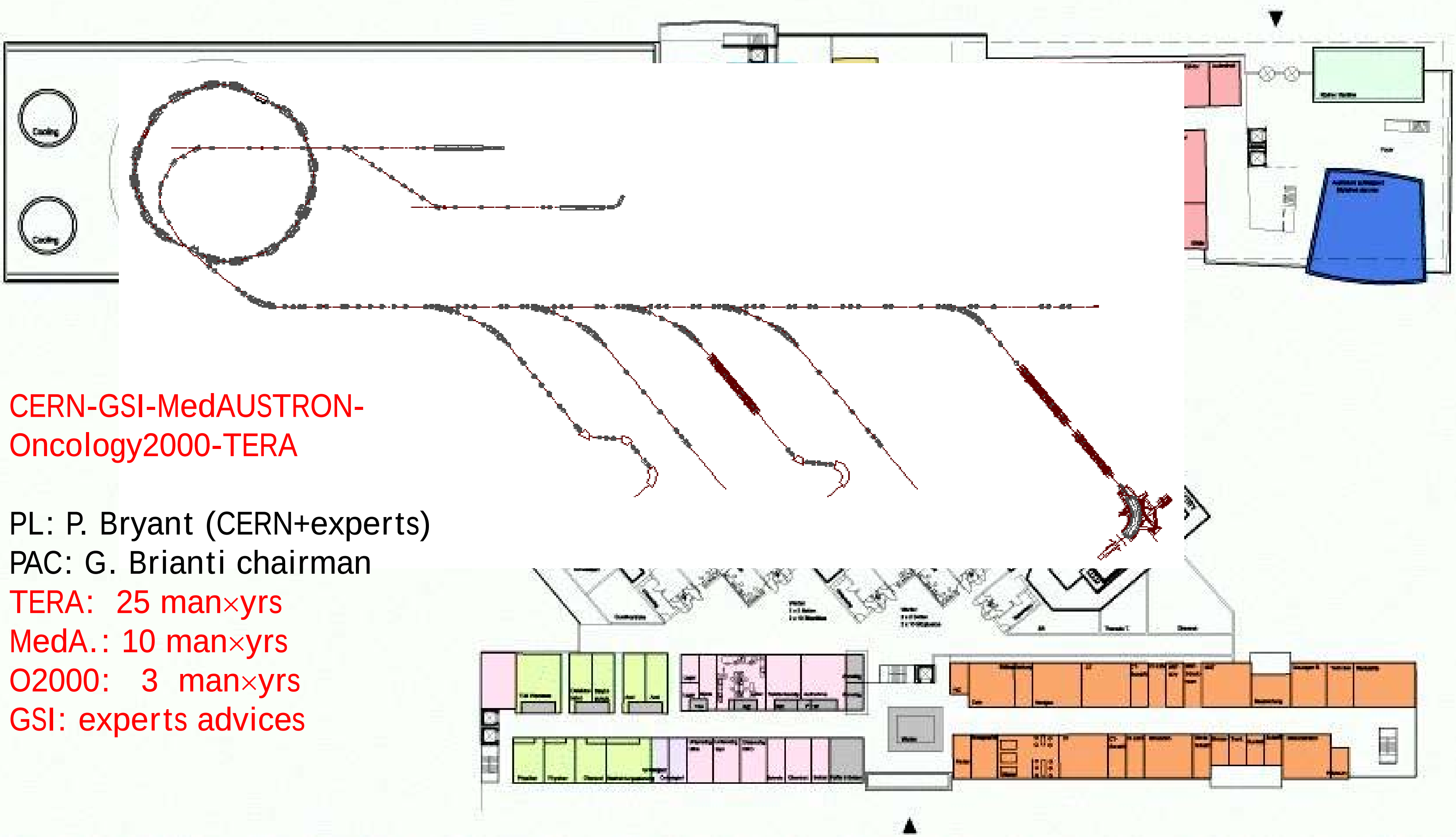
Year 1991...

ATER-INFN

TERA
Fondazione per Adroterapia Oncologica

From 1996 to 1999 at CERN

PIMMS (Proton-Ions Medical Machine Study)



CERN-GSI-MedAUSTRON-Oncology2000-TERA

PL: P. Bryant (CERN+experts)
PAC: G. Brianti chairman
TERA: 25 man×yrs
MedA.: 10 man×yrs
O2000: 3 man×yrs
GSI: experts advices

Objective: define the optimal hadrontherapy centre without constraints

fondazione CNAO

Not-for-profit private Foundation

Created by the Italian Ministry of Health at the beginning of 2001

with the purpose to build and run a hadrontherapy Centre

The Board is formed by 13 Institutions:

- 5 hospitals
- 3 universities
- 2 research institutes
- 2 public entity (Ministry of Health and Town of Pavia)
- 1 bank foundation

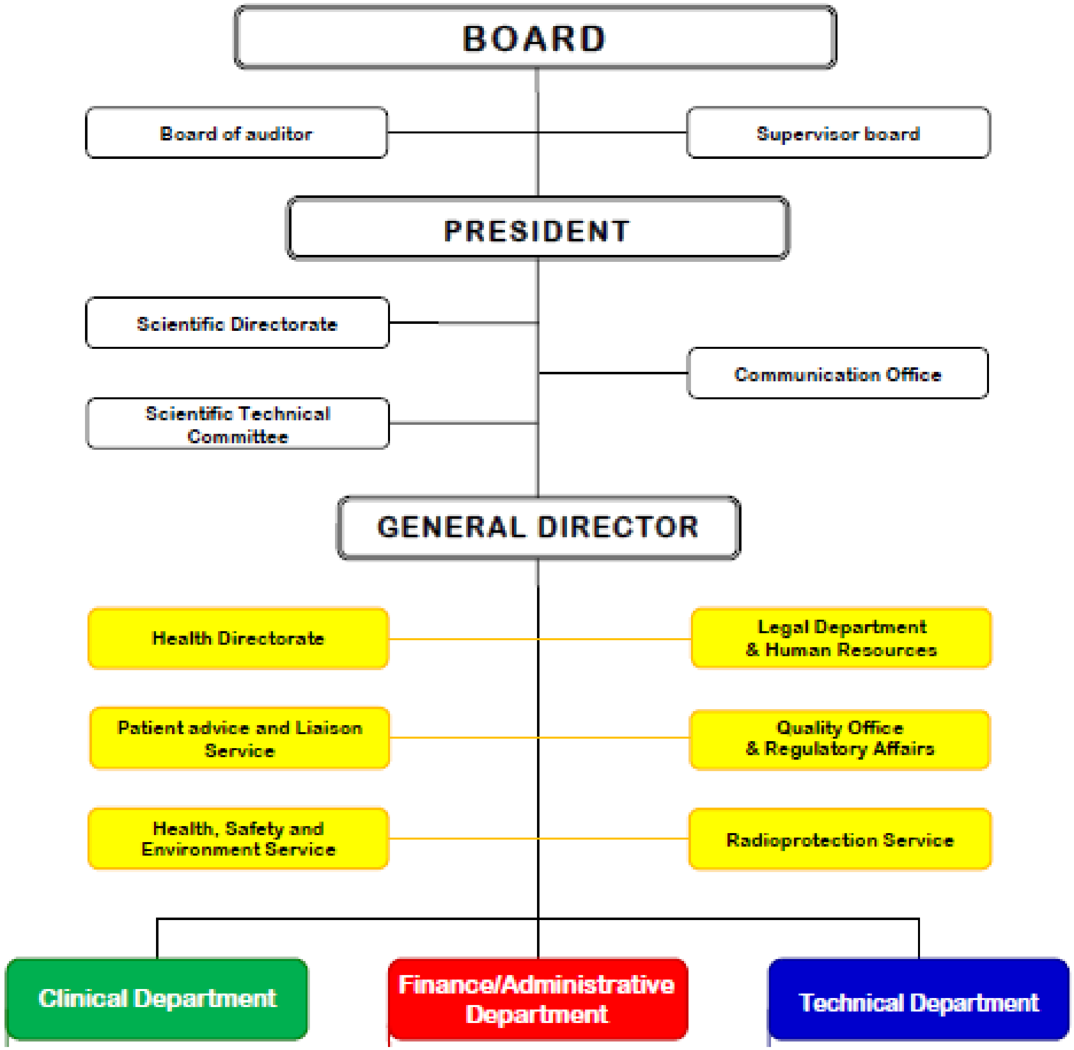
Phases of CNAO

Phase 0: organization → Years: 2002 - 2004

Phase 1: construction → Years : 2005 - 2010

Phase 2: experimental → Years: 2010 - 2013

Phase 3: running → Years: 2014 - …



Synchrotron Operation: H24, 7/7
Maintenance: 4/year - 5 days each (Thursday to Tuesday)
Treatments: Mon to Fri - 8:00 to 21:00
QA: Mon to Fri - 6:00 to 8:00
Beam time for research during nights and week-ends

Collaborating Institutes: a network for construction and research

NATIONAL

TERA Foundation: final design and high tech specifications

INFN: technical issues, radiobiology, research, formation

University of Milan: medical coordination and formation

University of Pavia: technical issues, radiobiology, formation

University of Catania: medical physics

University of Florence: medical physics

University of Turin: interface beam-patient, TPS

Polytechnic of Milan: patient positioning, radioprotection, authorisations

European Institute of Oncology: medical activities, authorisations

San Matteo Foundation: medical activities, logistics

Town of Pavia: land and authorisations

Province of Pavia: logistics and authorisation

Collaborating Institutes: a network for construction and research

INTERNATIONAL

CERN (Geneva): technical tasks, PIMMS

GSI (Darmstadt): linac and special components

LPSC (Grenoble): technical tasks

Med-Austron (Wien): technical and clinical collaboration

Roffo Institute (Buenos Aires): medical activities

NIRS (Chiba): medical activities, radiobiology, formation

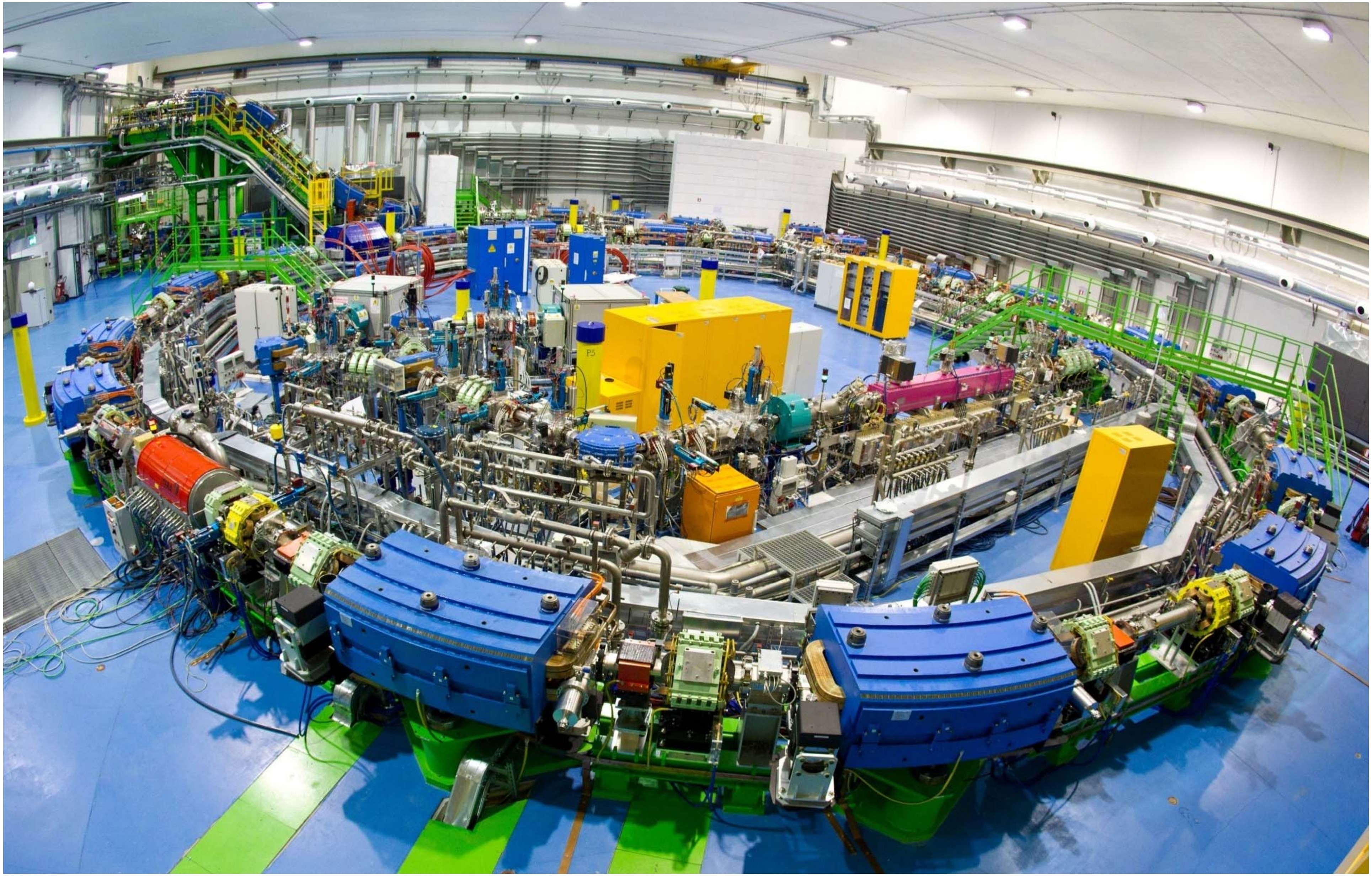
HIT (Heidelberg): research issues

IFJ PAN (Krakow - Poland): medical activities

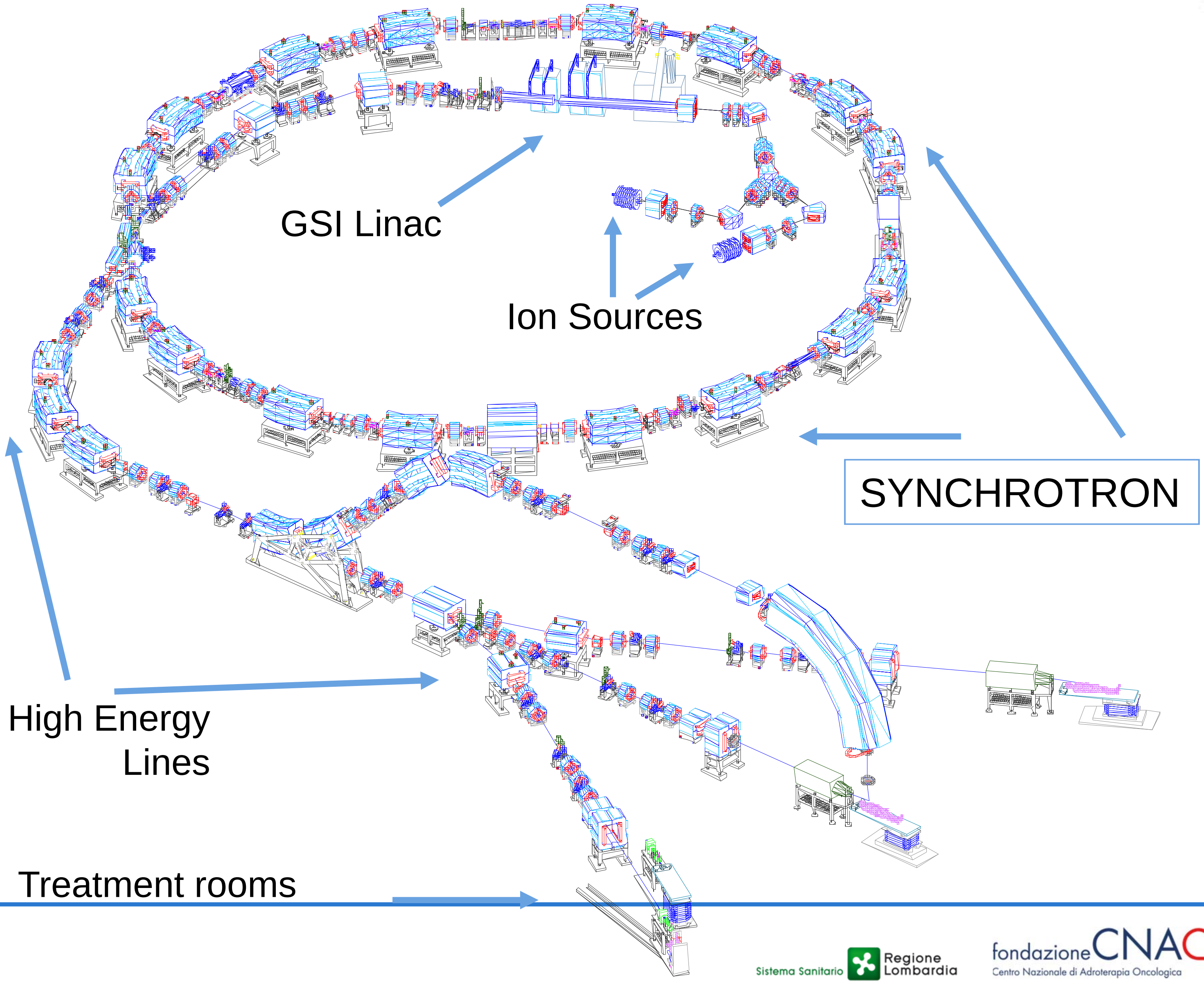
Uni Essen (Germany): medical activities

Sykehuspartner (Norway): medical activities

The high-tech for protons and carbon ions

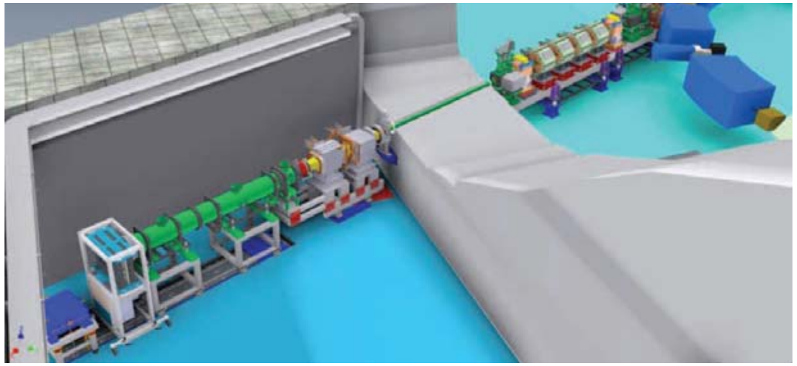


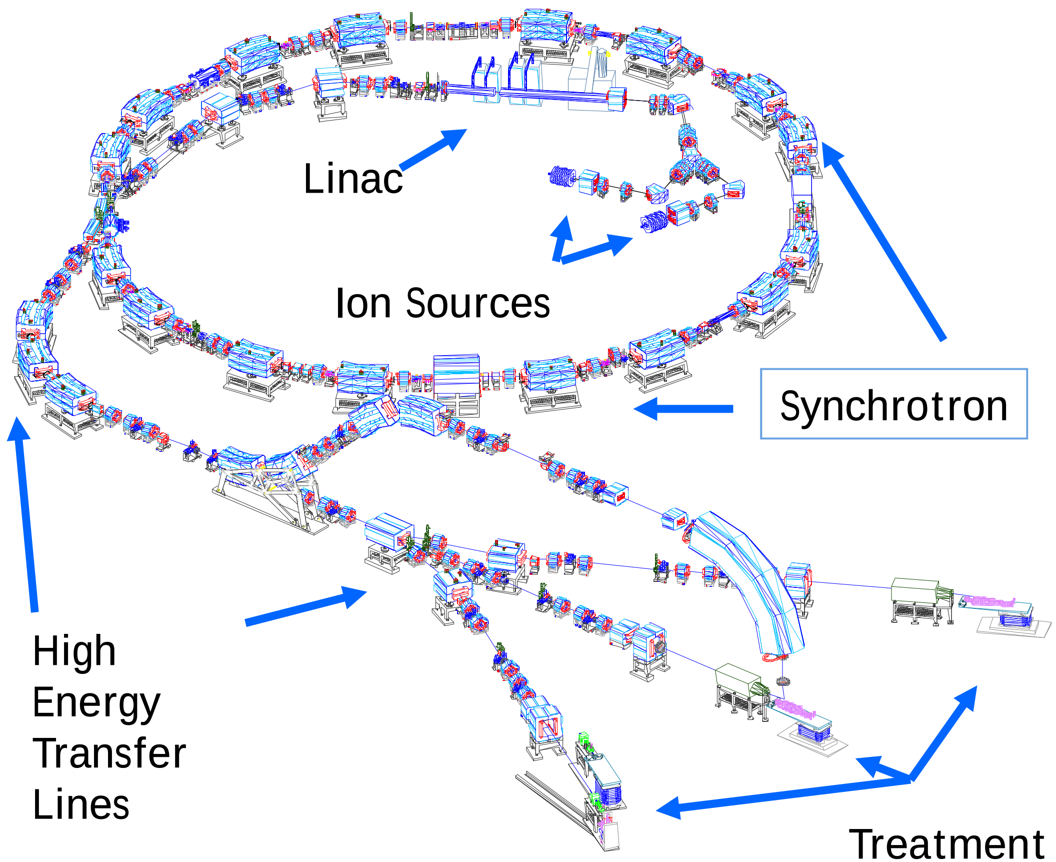
CNAO System - A prototype



Flexible hightech design: compact solution

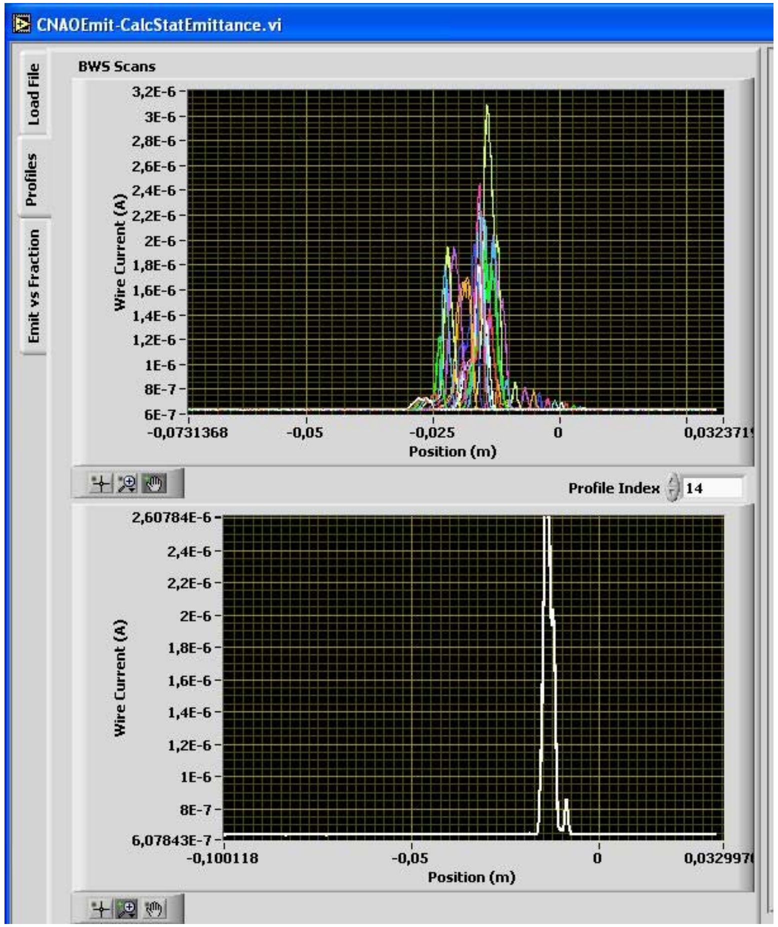
Coming up in 2018
New experimental room
(in collaboration with INFN)

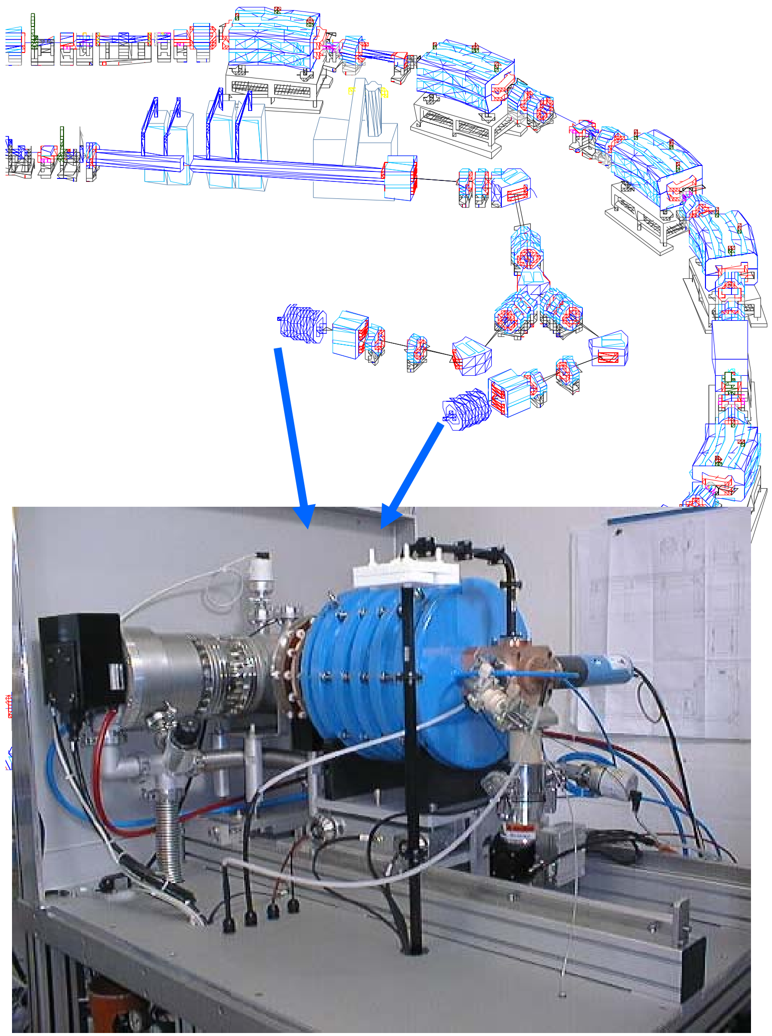




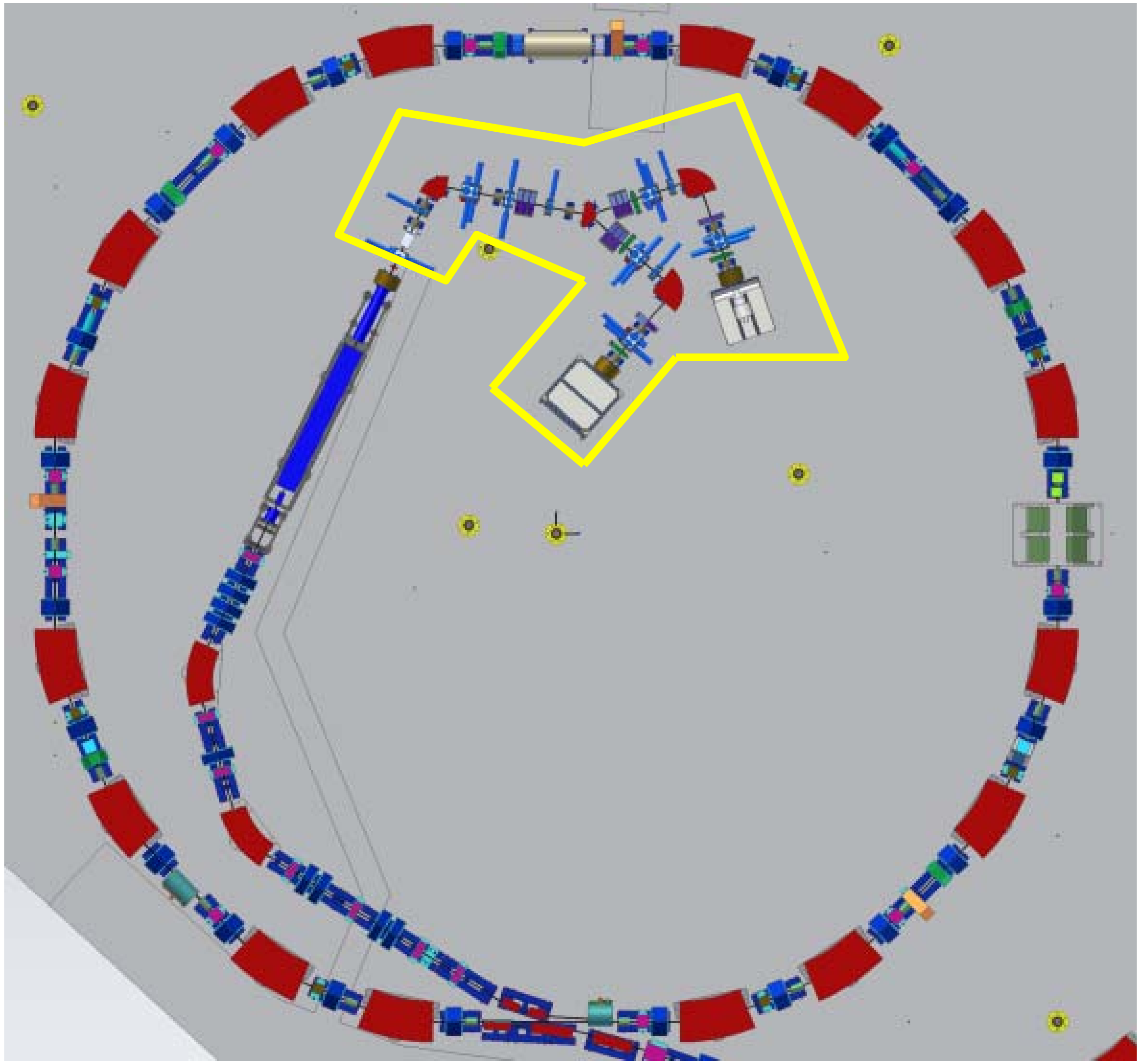
Hospital based:
safety, efficiency, reliability, maintainability

Ion sources: where protons and carbon ions are generated





Each source produces a cloud formed by 1 billion of carbon ions or 10 billions of protons



LEBT

0.008 MeV/u H^{3+}
0.008 MeV/u C^{4+}

I ~ 0.5 mA (H^{3+})
I ~ 0.2 mA (C^{4+})

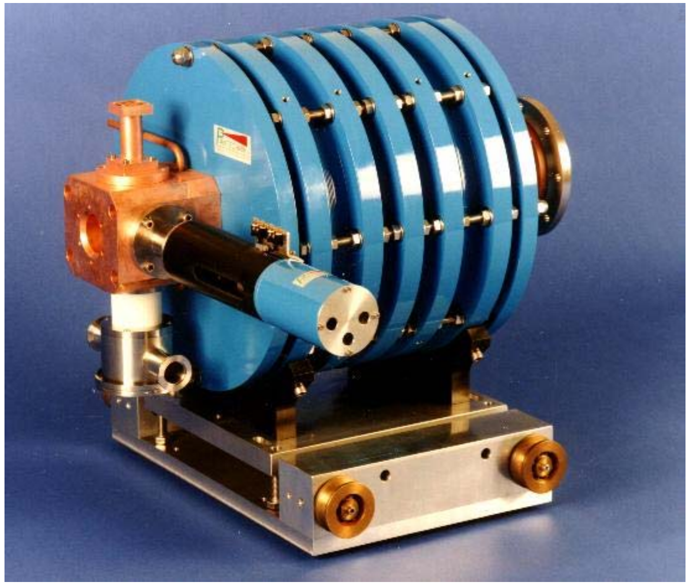
Two ECR sources

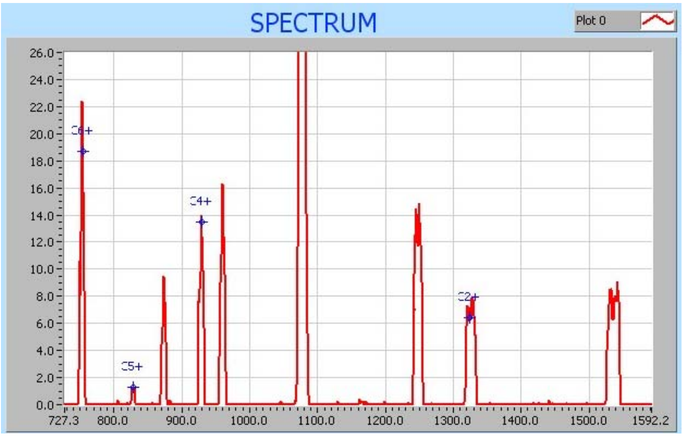
Continuous beam

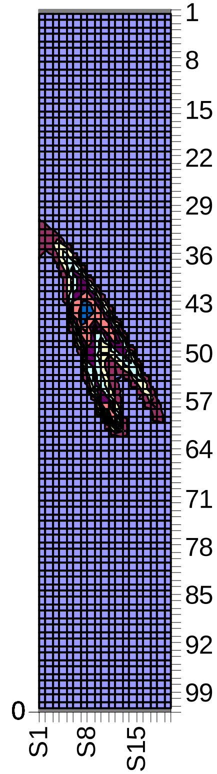
LEBT Chopper

Ion sources

ECR, always on

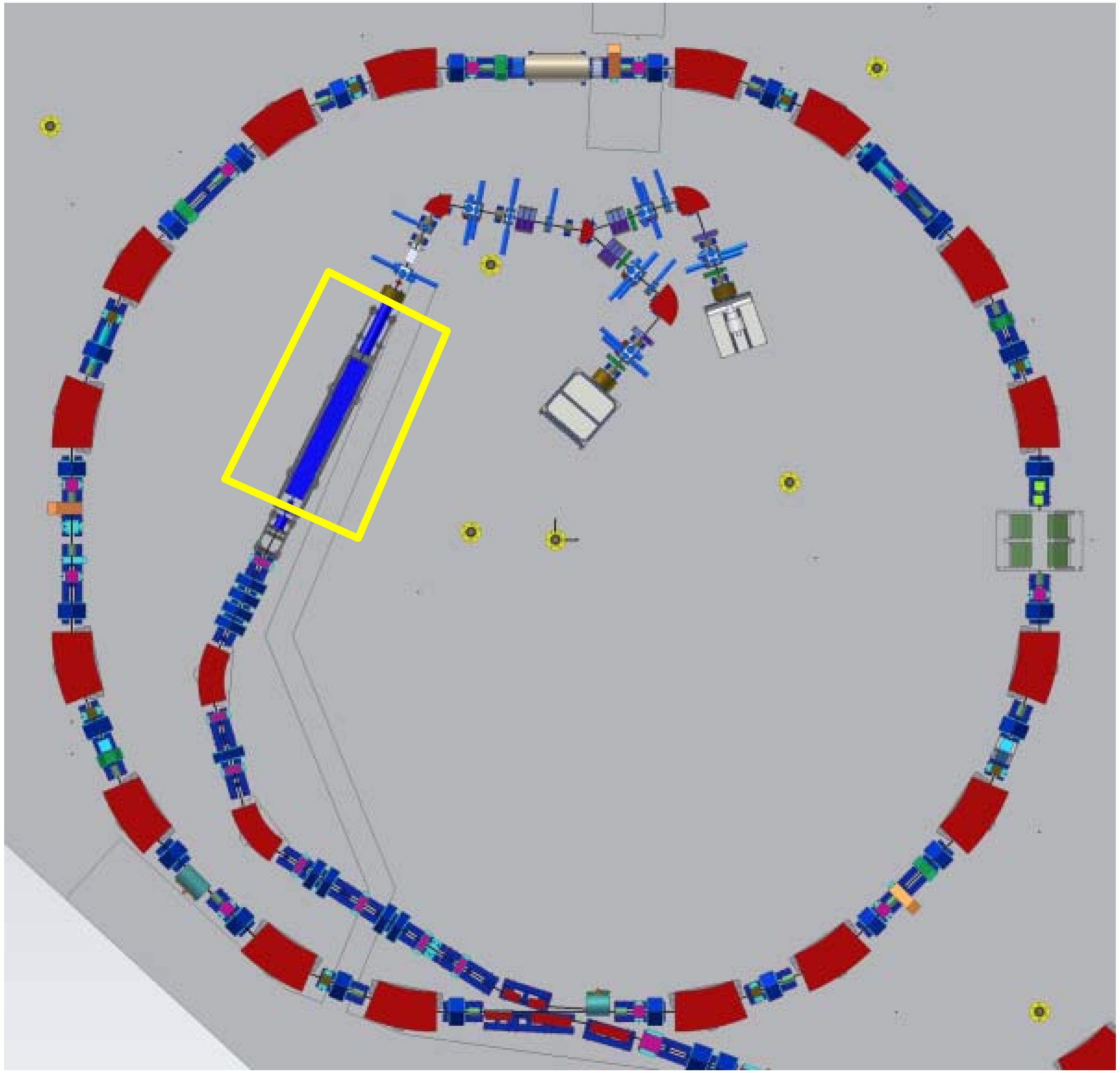






$I_{tot} = 250\ \mu A$

$I_{180\pi} = 85\%\ I_{tot}$



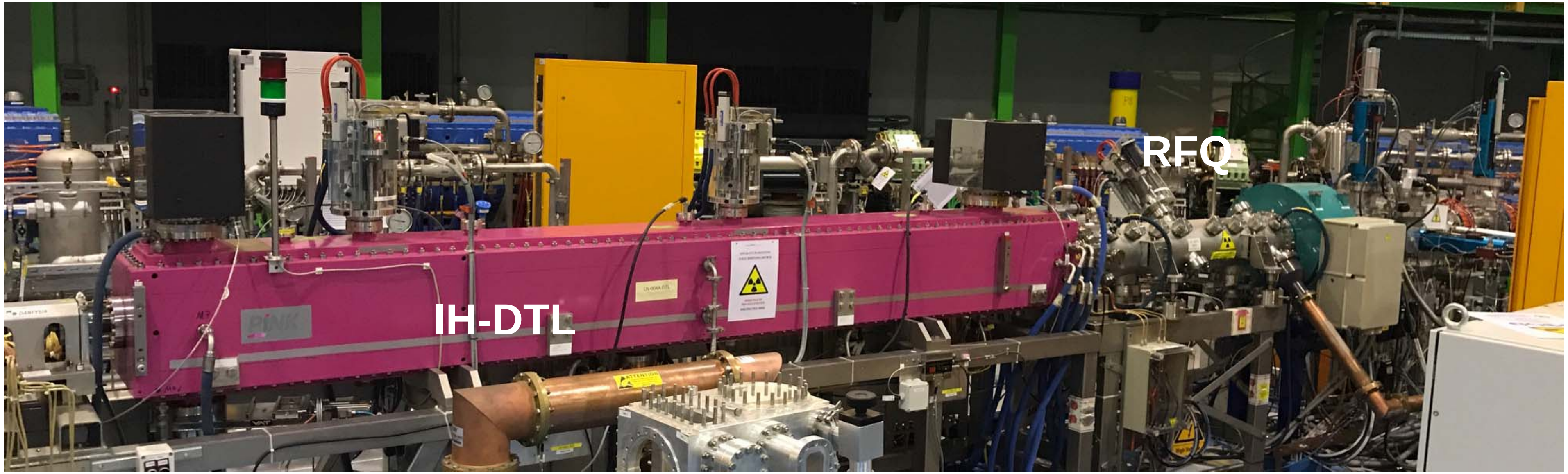
Linac=RFQ+IH

217 MHz

RFQ
0.008-0.4 MeV/u H^{3+}
0.008-0.4 MeV/u C^{4+}

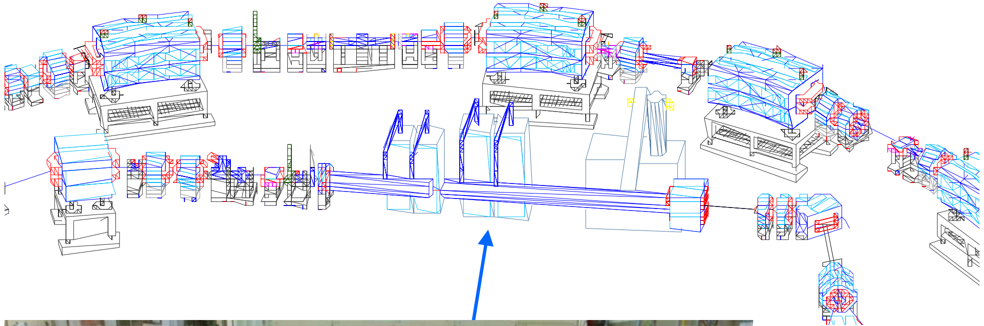
IH
0.4-7 MeV/u H^{3+}
0.4-7 MeV/u C^{4+}

CNAO Injector

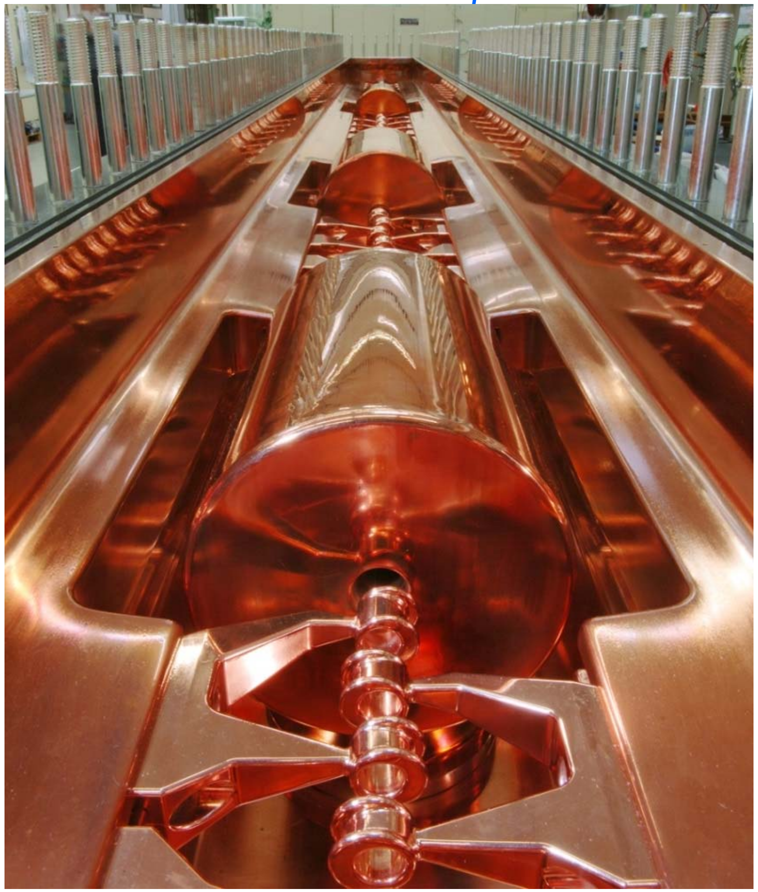


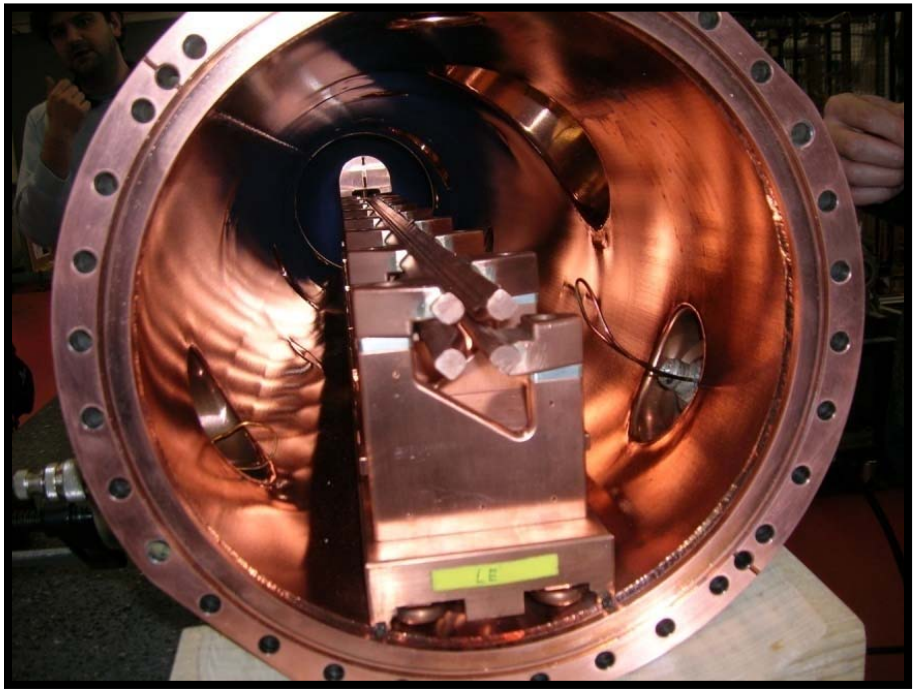
The injector consists of several distinct parts:
– The *Ion Source*, which creates the beam.
– The *Low Energy Beam Transport* (LEBT) takes the beam from the ion source to the first accelerating structure.
– The *RadioFrequency Quadrupole* (RFQ) is the first accelerating stage that increases the energy whilst maintaining strong focussing.
– The *Linear Accelerator* (Linac) provides greater acceleration with less focussing.

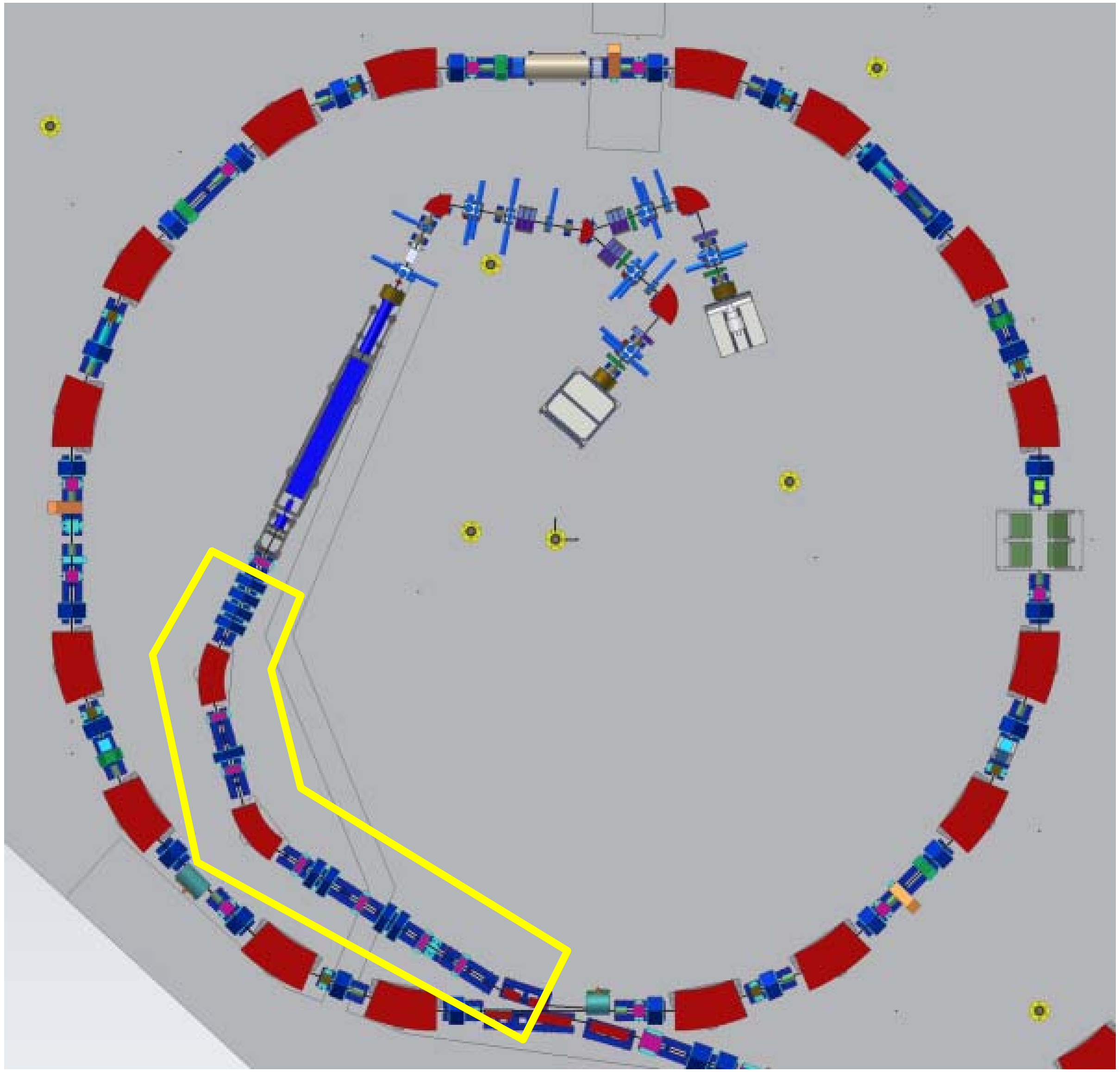
The Linear accelerator for ions



In about 6 meters the beam increases the energy by a factor 1000 – to reach 1/10th of light speed… 30'000 km/sec







MEBT

7 MeV p
7 MeV/u C^{6+}

I ~ 0.75 mA (p)
I ~ 0.12 mA (C^{6+})

Stripping foil

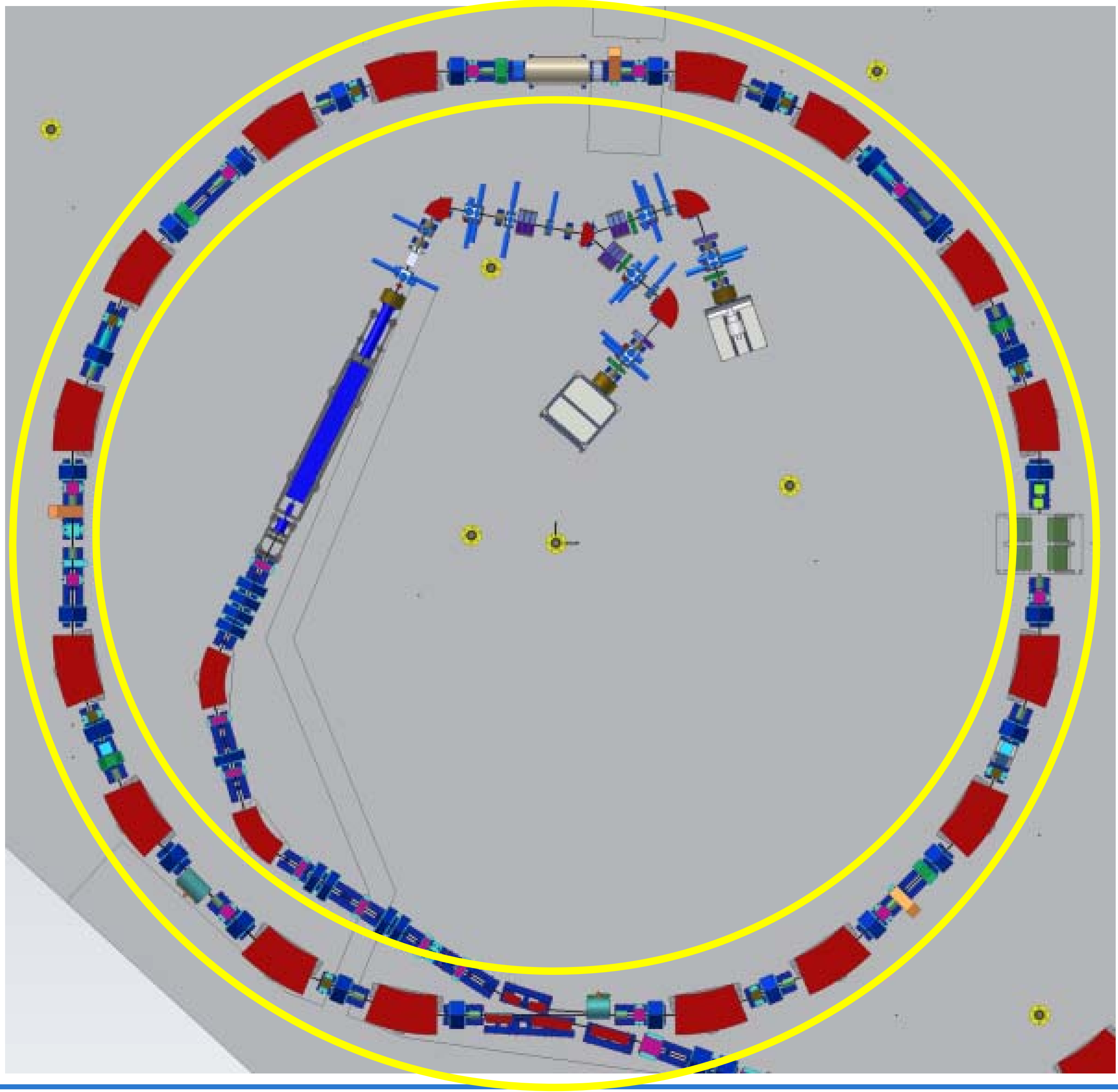
Current selection

Debuncher

Emittance dilution

Match betas

$(x,x')_{Inj}$



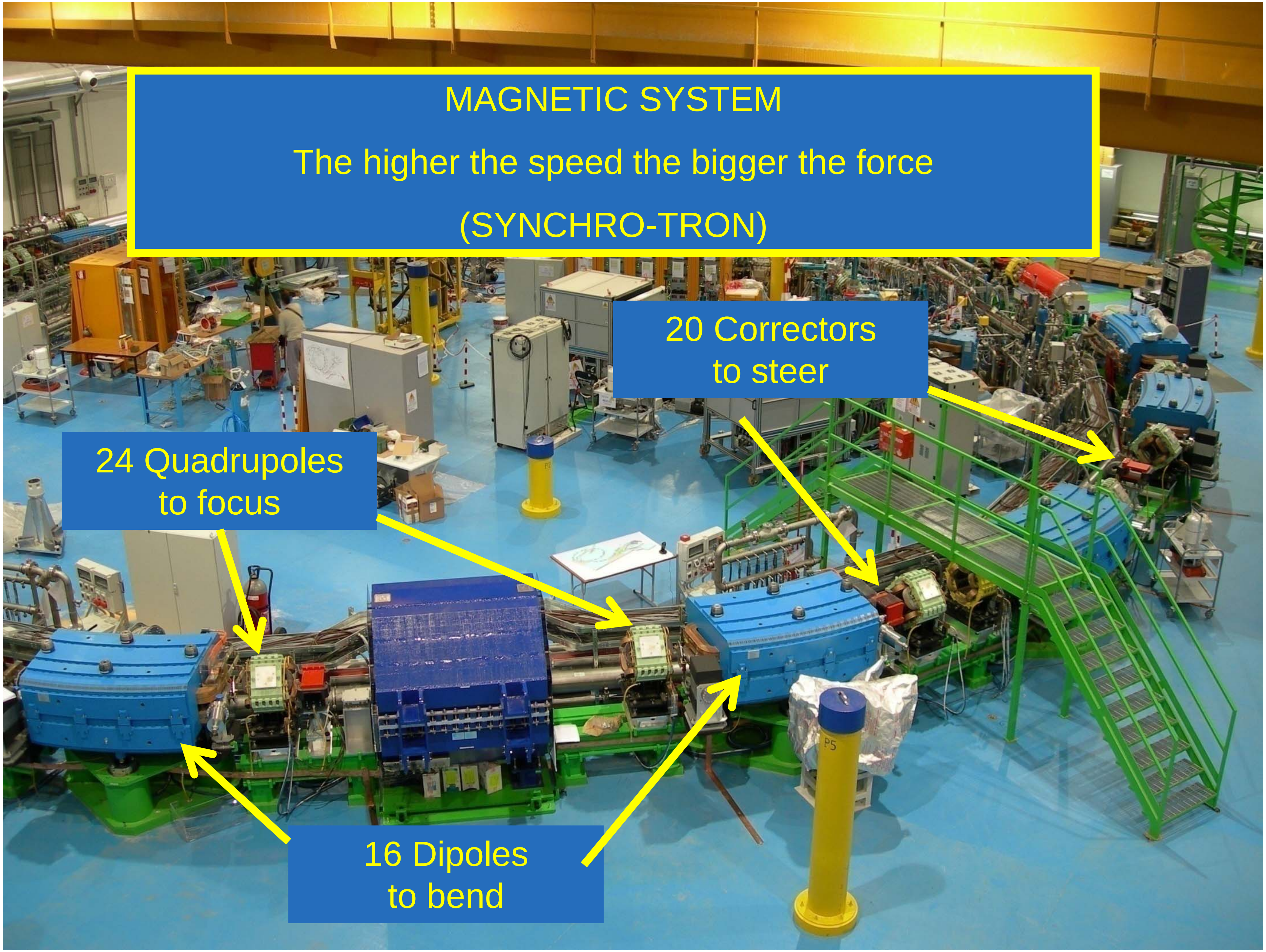
Synchrotron

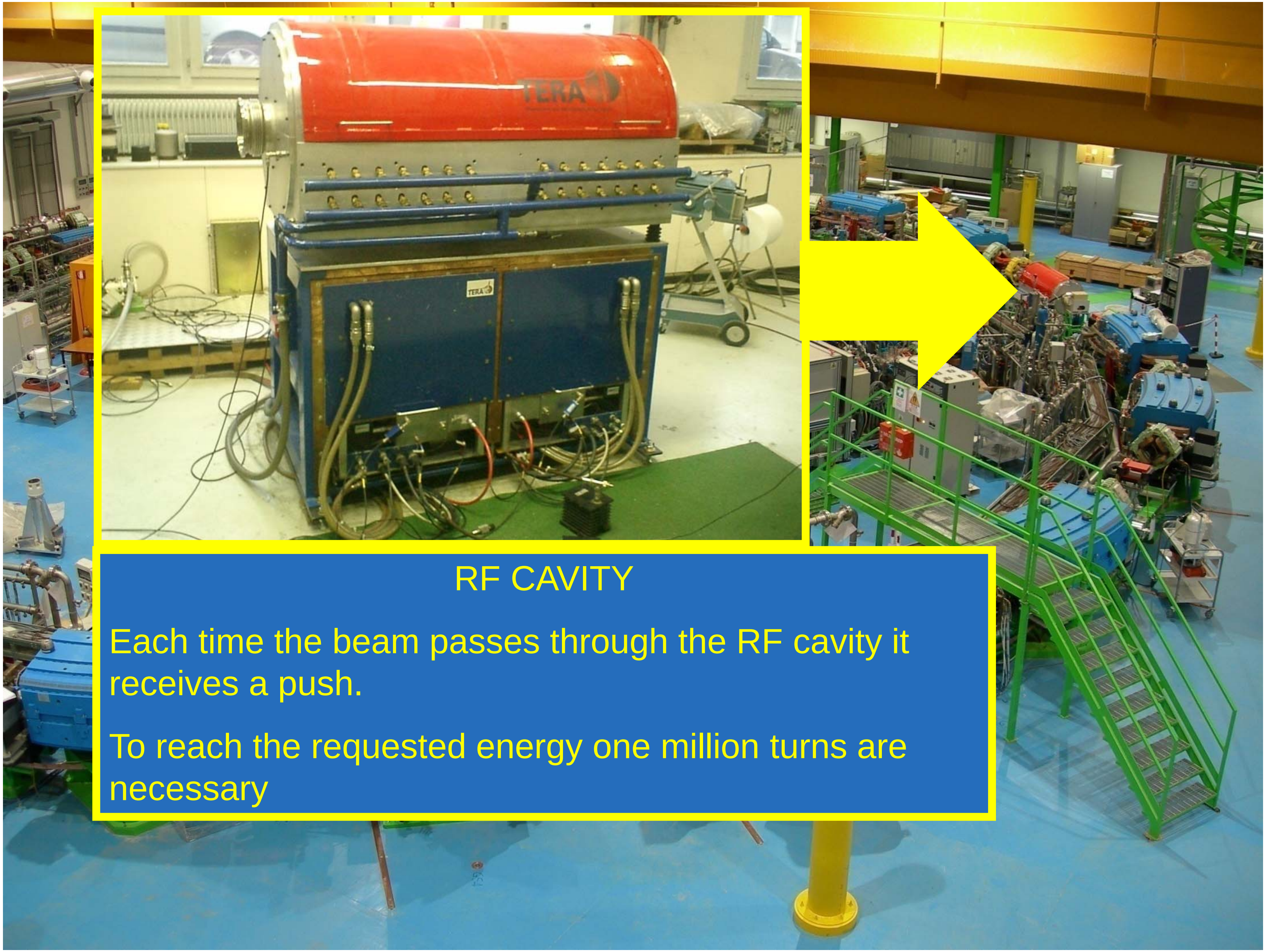
7-250 MeV p
7-400 MeV/u C

I ~ 0.1-5 mA (p)
I ~ 0.03-1.5 mA (C)

Slow extraction

Betatron core

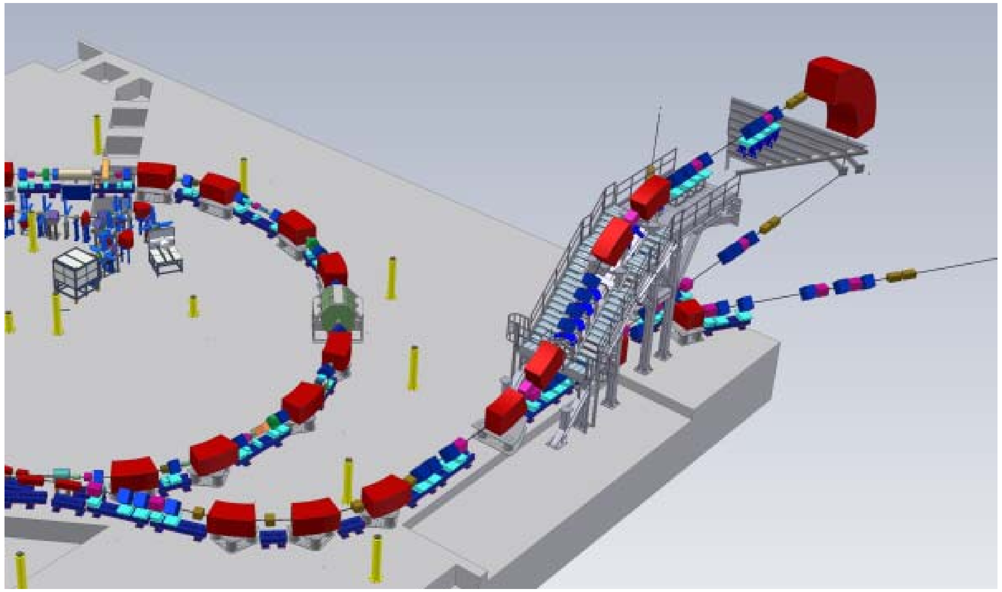

MAGNETIC SYSTEM
The higher the speed the bigger the force
(SYNCHRO-TRON)
20 Correctors
to steer
24 Quadrupoles
to focus
16 Dipoles
to bend

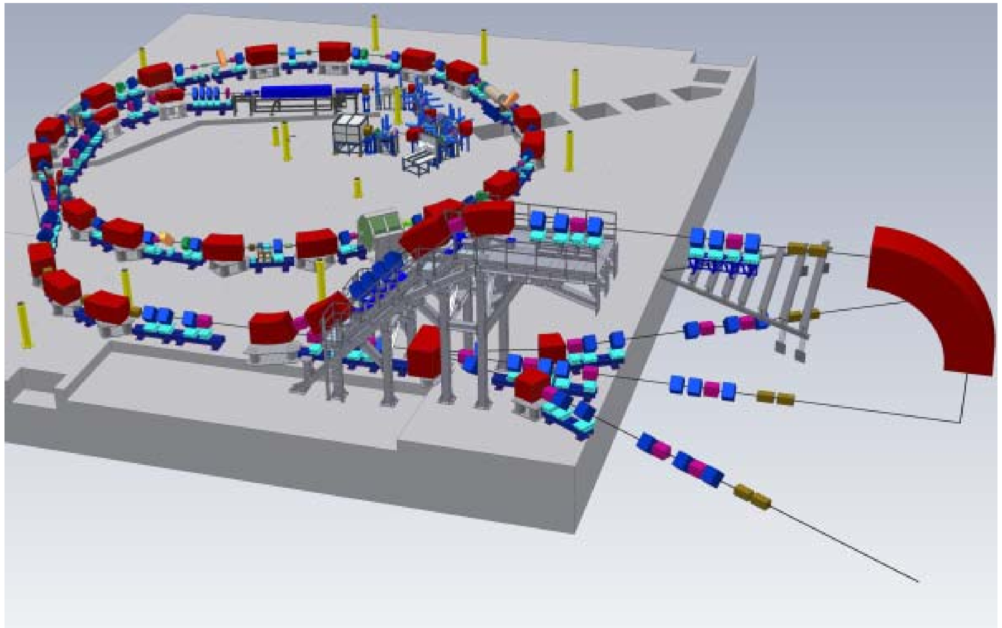


RF CAVITY

Each time the beam passes through the RF cavity it receives a push.

To reach the requested energy one million turns are necessary





HEBT

60-250 MeV p
120-400 MeV/u C

10^{10} p/spill (~2nA)
4 10^{8} C/spill (~0.4nA)

Different settings for

- Treatment Line
- Horizontal beam size
- Vertical beam size
- Extraction energy

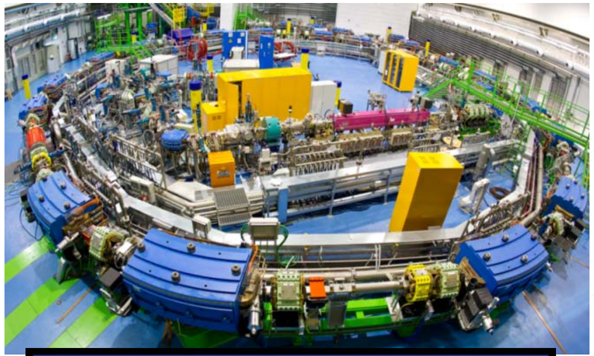
Vertical beam line

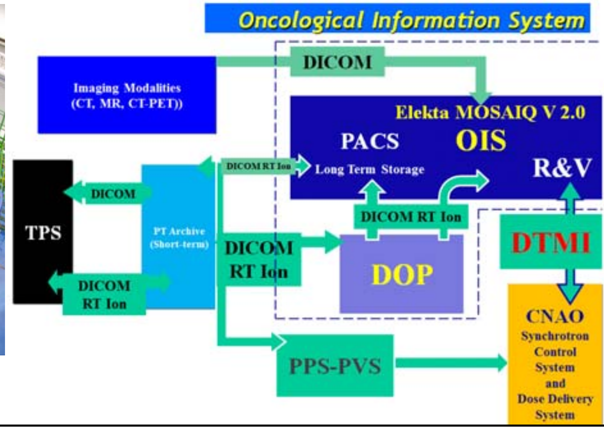
Vertical beam line: 90° bending magnet

High precision devices for patient positioning

Collaboration CNAO-PoliMi

"LEGO Model": integrated technical and medical solutions

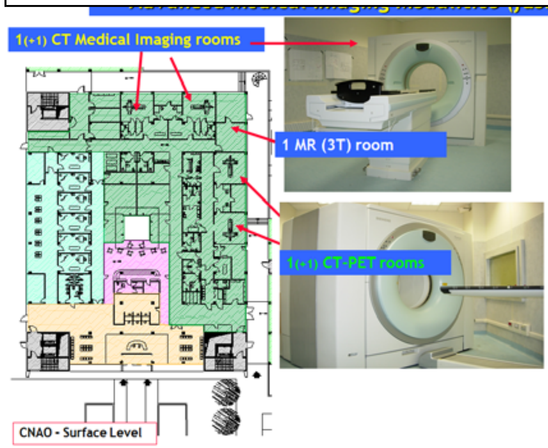


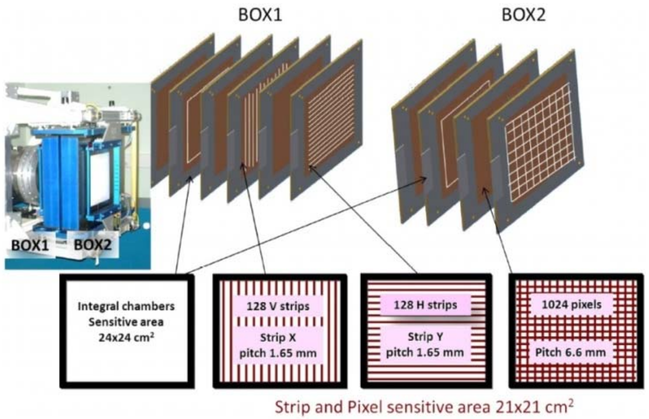


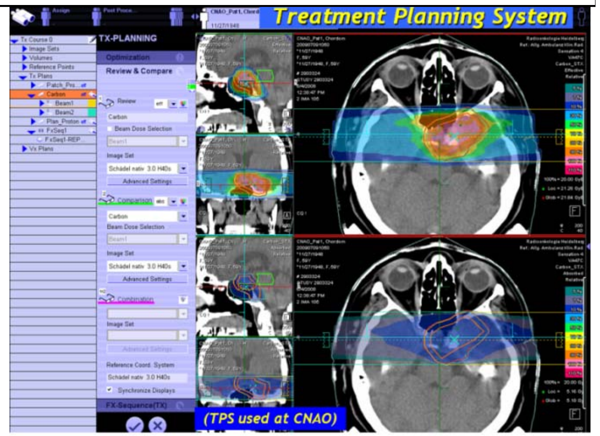
The real challenge:

make ALL systems running together

safely, efficiently, reliably and easily maintainable.







Sistema Sanitario Regione Lombardia
fondazione CNAO Centro Nazionale di Adroterapia Oncologica

CNAO Certifications ISO 9001 and ISO 13485

CERTIFICATO

Nr 50 100 11355/B - Rev. 04

Si attesta che / *This is to certify that*

IL SISTEMA QUALITÀ DI
THE QUALITY SYSTEM OF

Fondazione CNAO

SEDE LEGALE E OPERATIVA:
REGISTERED OFFICE AND OPERATIONAL SITE:

STRADA PRIVATA CAMPEGGI 53
I-27100 PAVIA (PV)

È CONFORME AI REQUISITI DELLA NORMA
HAS BEEN FOUND TO COMPLY WITH THE REQUIREMENTS OF

UNI CEI EN ISO 13485:2016
SISTEMI QUALITÀ – DISPOSITIVI MEDICALI
QUALITY SYSTEMS – MEDICAL DEVICES

QUESTO CERTIFICATO È VALIDO PER IL SEGUENTE CAMPO DI APPLICAZIONE
THIS CERTIFICATE IS VALID FOR THE FOLLOWING SCOPE

Progettazione, sviluppo ed assistenza tecnica di sistemi e dispositivi di trattamento adroterapico e di radioterapia guidata da immagini

Design, development and technical support of systems and devices used in hadrontherapy and in image guided radiotherapy

PER INFORMAZIONI PUNTUALI E AGGIORNATE CIRCA EVENTUALI VARIAZIONI INTERVENUTE NELLO STATO DELLA CERTIFICAZIONE DI CUI AL PRESENTE CERTIFICATO, SI PREGA DI CONTATTARE IL N° TELEFONICO 02 241301 O INDIRIZZO E-MAIL TUV.MS@TUV.IT

ACCREDIA
L'ENTE ITALIANO DI ACCREDITAMENTO

SGQ N° 049A SSI N° 005G PRD N° 081B
SGA N° 018D ITX N° 001L ISP N° 057E
SCR N° 009F PRS N° 077C LAB N° 0076

Membro degli Accordi di Mutuo Riconoscimento EA, IAF e ILAC
Signatory of EA, IAF and ILAC Mutual Recognition Agreements

Per l'Organismo di Certificazione
For the Certification Body
TÜV Italia S.r.l.

Andrea Coscia
Direttore Divisione Management Service

Validità /*Validity*	
Dal / From:	**2017-08-02**
Al / To:	**2018-07-26**
Data emissione / *Printing Date*	**2017-08-02**

PRIMA CERTIFICAZIONE / *FIRST CERTIFICATION*: **2012-07-27**

"LA VALIDITÀ DEL PRESENTE CERTIFICATO È SUBORDINATA A SORVEGLIANZA PERIODICA A 12 MESI E AL RIESAME COMPLETO DEL SISTEMA DI GESTIONE AZIENDALE CON PERIODICITÀ TRIENNALE"

"THE VALIDITY OF THE PRESENT CERTIFICATE DEPENDS ON THE ANNUAL SURVEILLANCE EVERY 12 MONTHS AND ON THE COMPLETE REVIEW OF COMPANY'S MANAGEMENT SYSTEM AFTER THREE-YEARS"

TÜV Italia S.r.l. • Gruppo TÜV SÜD • Via Carducci 125, Pal. 23 • 20099 Sesto San Giovanni (MI) • Italia • www.tuv.it

CERTIFICATO

Nr 50 100 11355/A - Rev. 02

Si attesta che / *This is to certify that*

IL SISTEMA QUALITÀ DI
THE QUALITY SYSTEM OF

Fondazione CNAO

SEDE LEGALE E OPERATIVA:
REGISTERED OFFICE AND OPERATIONAL SITE:

STRADA PRIVATA CAMPEGGI 53
I-27100 PAVIA (PV)

È CONFORME AI REQUISITI DELLA NORMA
HAS BEEN FOUND TO COMPLY WITH THE REQUIREMENTS OF

UNI EN ISO 9001:2008

QUESTO CERTIFICATO È VALIDO PER IL SEGUENTE CAMPO DI APPLICAZIONE
THIS CERTIFICATE IS VALID FOR THE FOLLOWING SCOPE

Erogazione di prestazioni medico specialistiche e di adroterapia in regime ambulatoriale e di prestazioni di diagnostica per immagini, finalizzate al trattamento adroterapico Ricerca clinica, radiobiologica, tecnologica applicata a servizi di adroterapia oncologica. Progettazione, sviluppo ed assistenza tecnica di sistemi e dispositivi di trattamento adroterapico e di radioterapia guidata da immagini (IAF 38, 19)

Outpatient provision of specialized health services, of hadrontherapy services and of diagnostic imaging services aimed hadrontherapy. Clinical, radiobiological and technological research applied to hadrontherapy services. Design, development and technical support of systems and devices used in hadrontherapy and in image guided radiotherapy (IAF 38, 19)

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Andrea Coscia
Direttore Divisione Management Service

Validità /*Validity*	
Dal / From:	**2016-01-07**
Al / To:	**2018-07-26**
Data emissione / *Printing Date*	**2016-01-07**

PRIMA CERTIFICAZIONE / *FIRST CERTIFICATION*: **2012-07-27**

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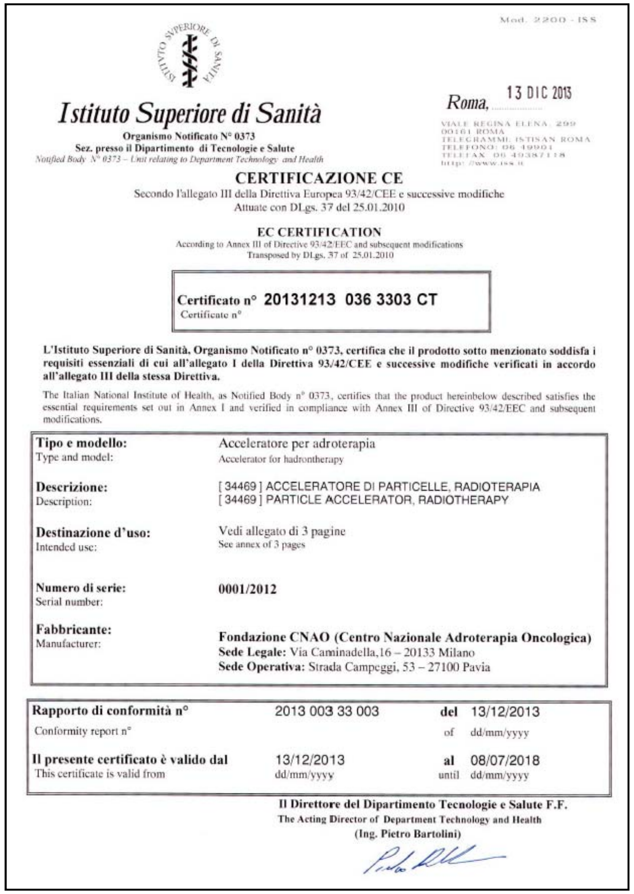
CNAO is Manufacturer of Medical Device (directive 93/42/EEC)

CNAO obtained the CE label after clinical experimentation



Mod. 2200 - ISS

Istituto Superiore di Sanità

Organismo Notificato N° 0373
Sez. presso il Dipartimento di Tecnologie e Salute
Notified Body N° 0373 – Unit relating to Department Technology and Health

Roma, 13 DIC 2013

VIALE REGINA ELENA, 299
00161 ROMA
TELEGRAMMI: ISTISAN ROMA
TELEFONO: 06 49901
TELEFAX 06 49387118
http: //www.iss.it

CERTIFICAZIONE CE
Secondo l'allegato III della Direttiva Europea 93/42/CEE e successive modifiche
Attuate con DLgs. 37 del 25.01.2010

EC CERTIFICATION
According to Annex III of Directive 93/42/EEC and subsequent modifications
Transposed by DLgs. 37 of 25.01.2010

Certificato n° 20131213 036 3303 CT
Certificate n°

L'Istituto Superiore di Sanità, Organismo Notificato n° 0373, certifica che il prodotto sotto menzionato soddisfa i requisiti essenziali di cui all'allegato I della Direttiva 93/42/CEE e successive modifiche verificati in accordo all'allegato III della stessa Direttiva.

The Italian National Institute of Health, as Notified Body n° 0373, certifies that the product hereinbelow described satisfies the essential requirements set out in Annex I and verified in compliance with Annex III of Directive 93/42/EEC and subsequent modifications.

Tipo e modello: Type and model:	Acceleratore per adroterapia Accelerator for hadrontherapy
Descrizione: Description:	[34469] ACCELERATORE DI PARTICELLE, RADIOTERAPIA [34469] PARTICLE ACCELERATOR, RADIOTHERAPY
Destinazione d'uso: Intended use:	Vedi allegato di 3 pagine See annex of 3 pages
Numero di serie: Serial number:	**0001/2012**
Fabbricante: Manufacturer:	**Fondazione CNAO (Centro Nazionale Adroterapia Oncologica)** **Sede Legale:** Via Caminadella,16 – 20133 Milano **Sede Operativa:** Strada Campeggi, 53 – 27100 Pavia

Rapporto di conformità n° Conformity report n°	2013 003 33 003	**del** of	13/12/2013 dd/mm/yyyy
Il presente certificato è valido dal This certificate is valid from	13/12/2013 dd/mm/yyyy	**al** until	08/07/2018 dd/mm/yyyy

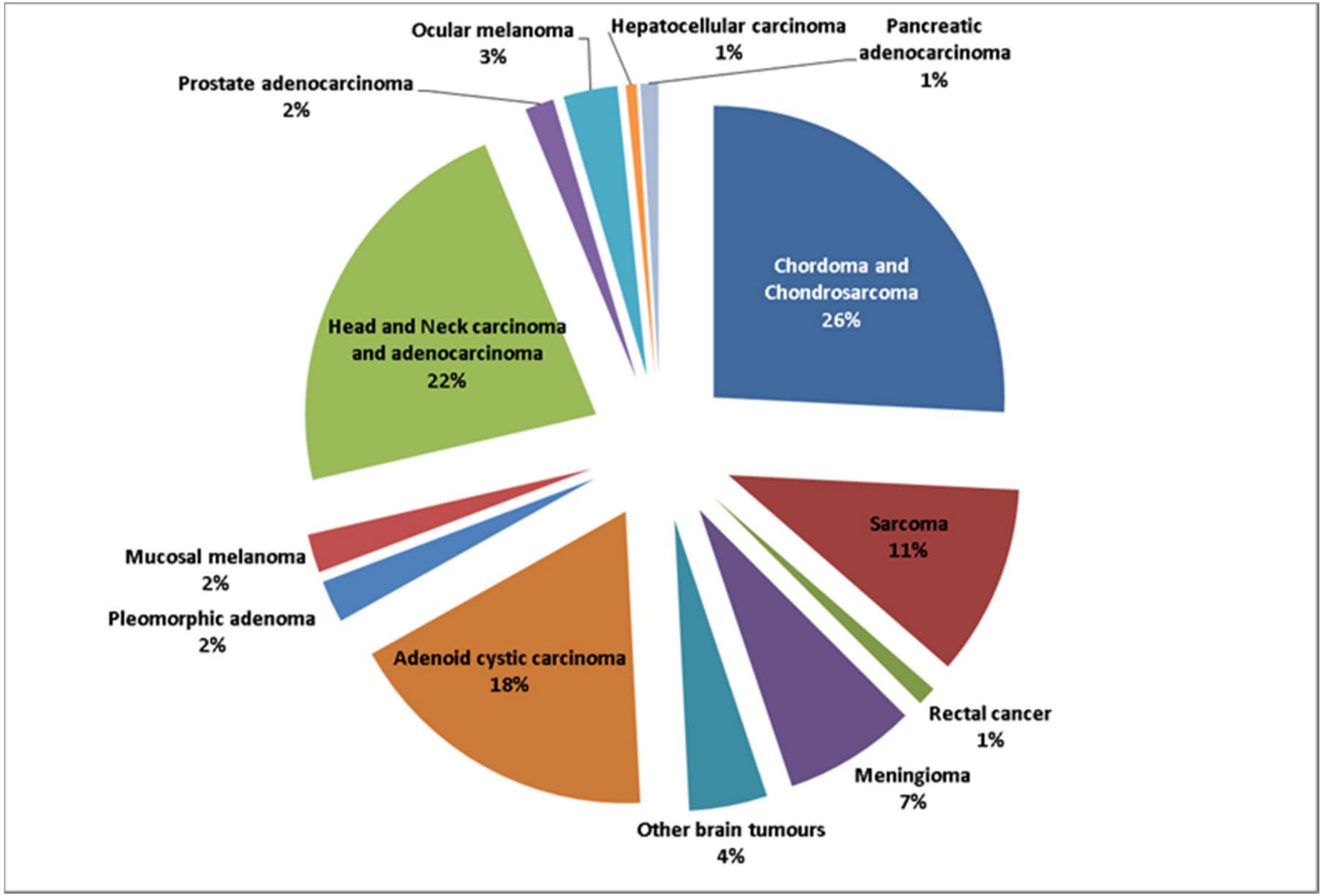
Il Direttore del Dipartimento Tecnologie e Salute F.F.
The Acting Director of Department Technology and Health
(Ing. Pietro Bartolini)

CE label is a good starting point to obtain FDA clearance fondazione CNAO

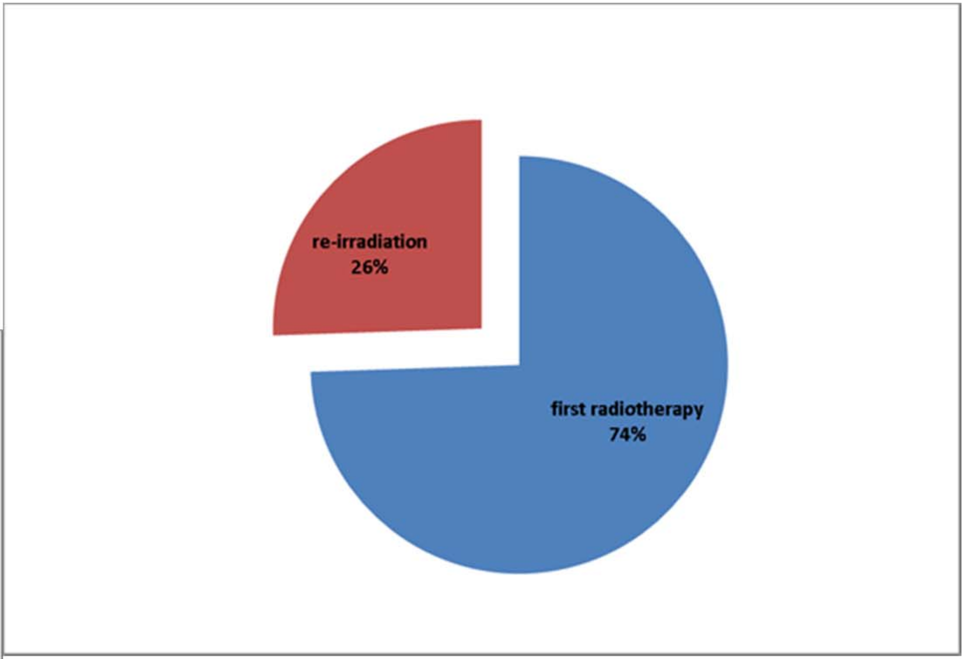
CNAOMed3.0

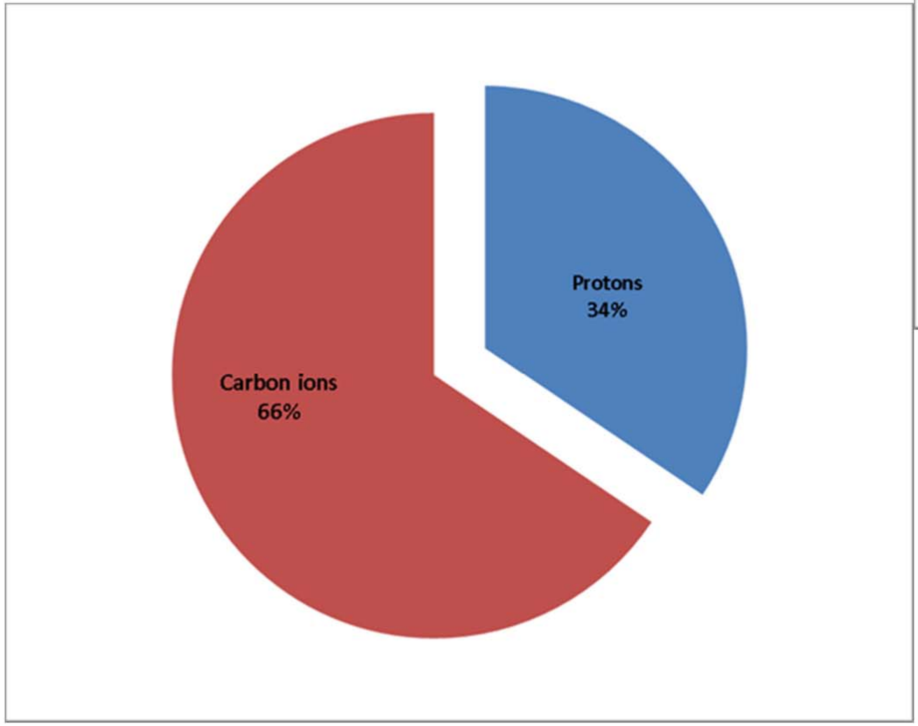
A MULTI-ION SOLUTION
THE LATEST ADVANCED THERAPY
TO FIGHT CANCER

Clinical Activity: Sites and Histology

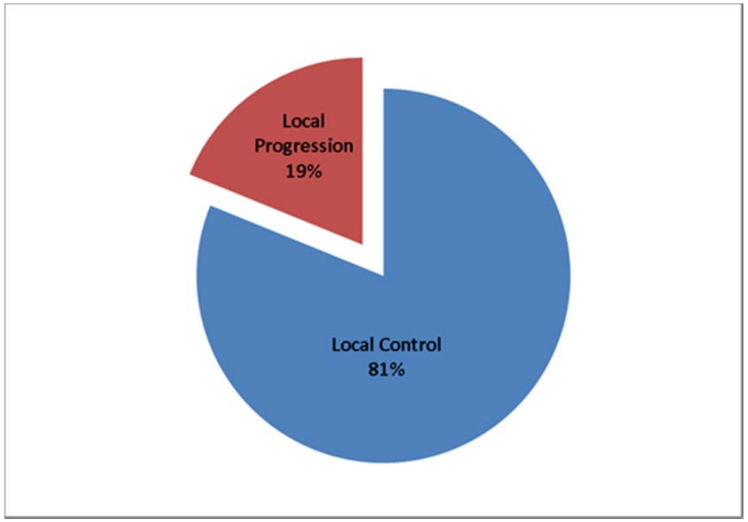


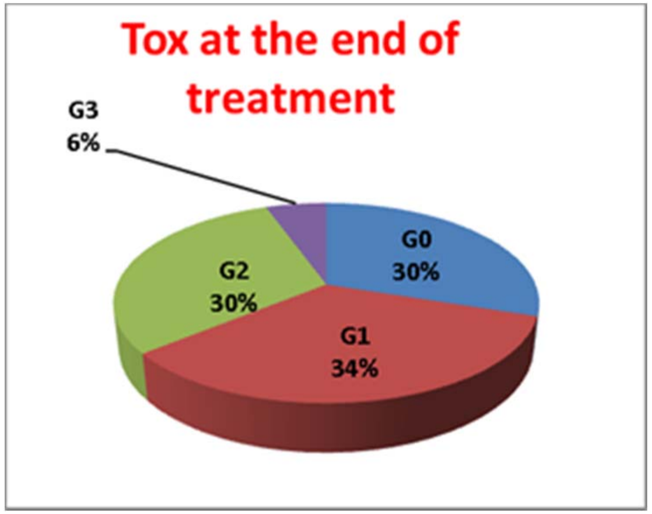
Overall Results

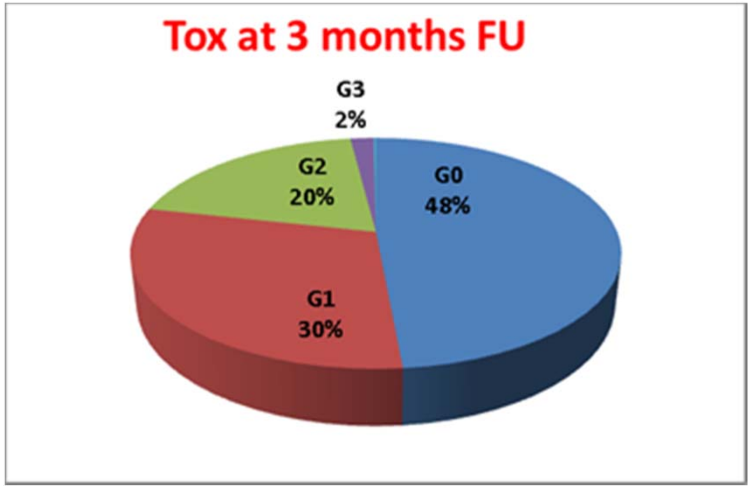


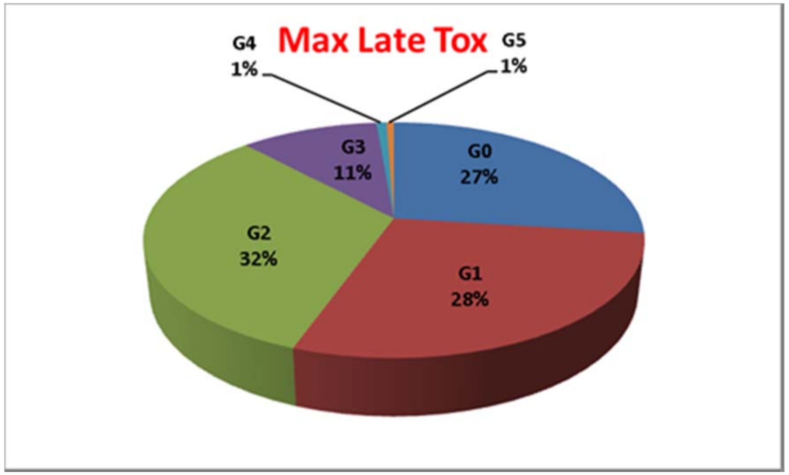


Overall Results



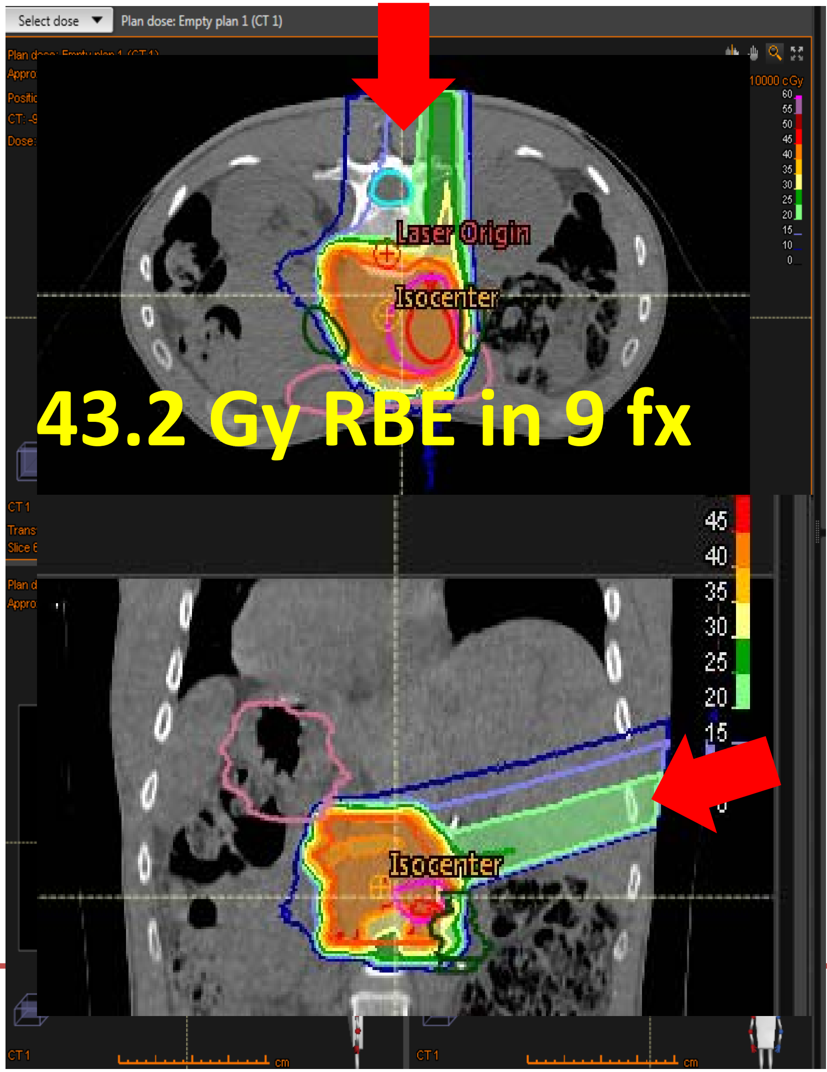




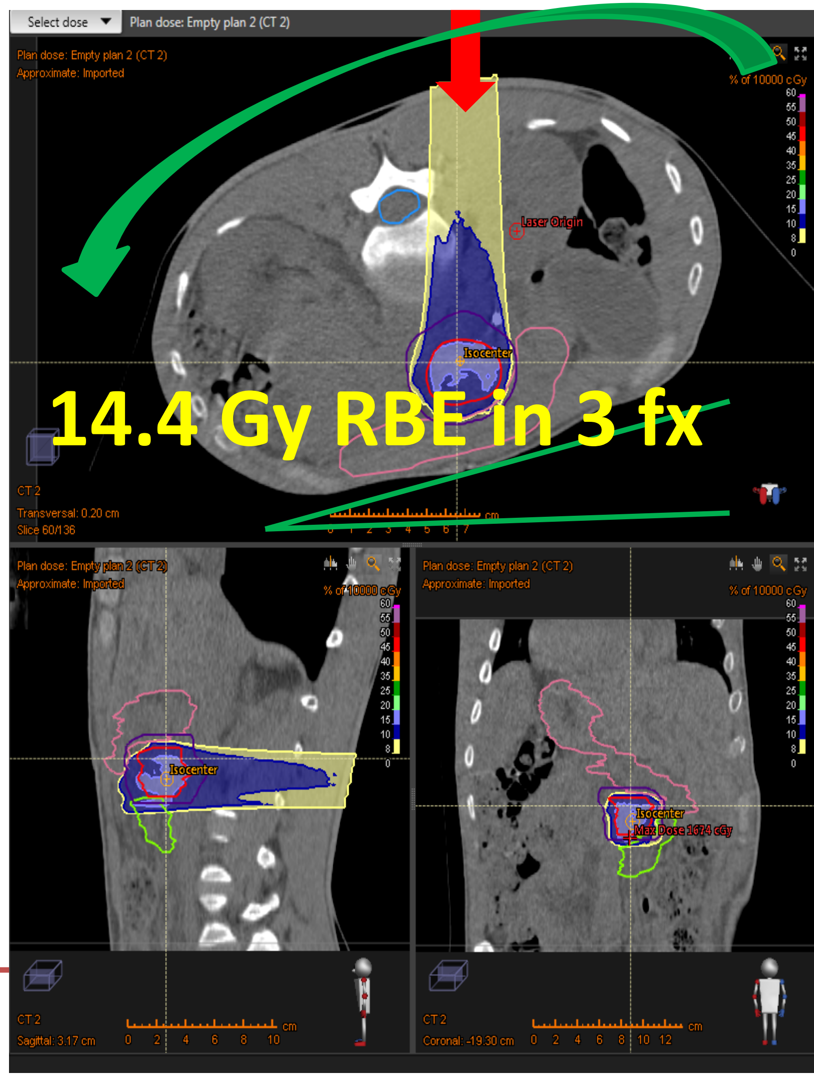


Pancreas cancer

CTV1 : Main tumor＋N2 nodes and plexus
9 fractions, prone position, 2 fields



CTV2 (Main tumor)
3 fractions, 1 field, rolled position

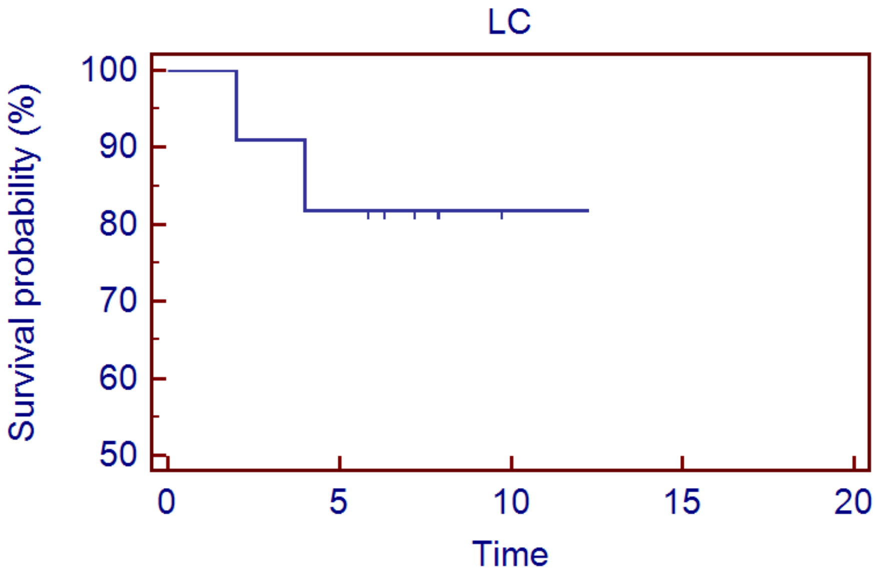


Locally advanced pancreas cancer

11 patients
After 6 months of chemotherapy (Gem/Gemox/Folfirinox)

Mean FU 12 months

CIRT: 57.6 GyE (12 fx)

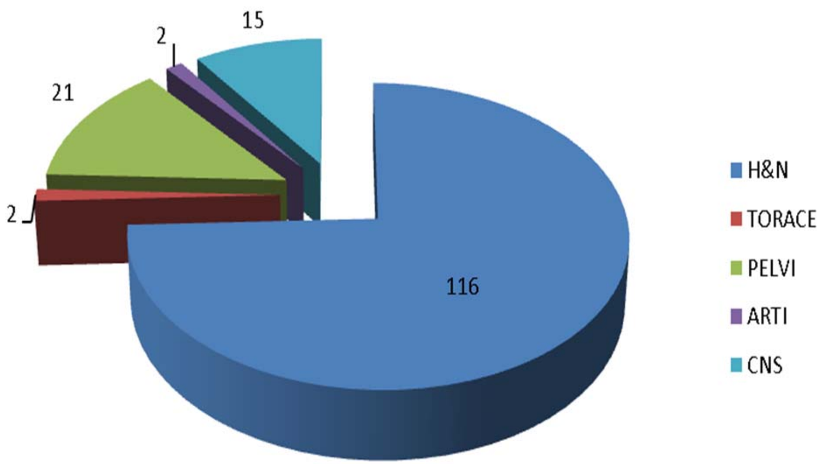


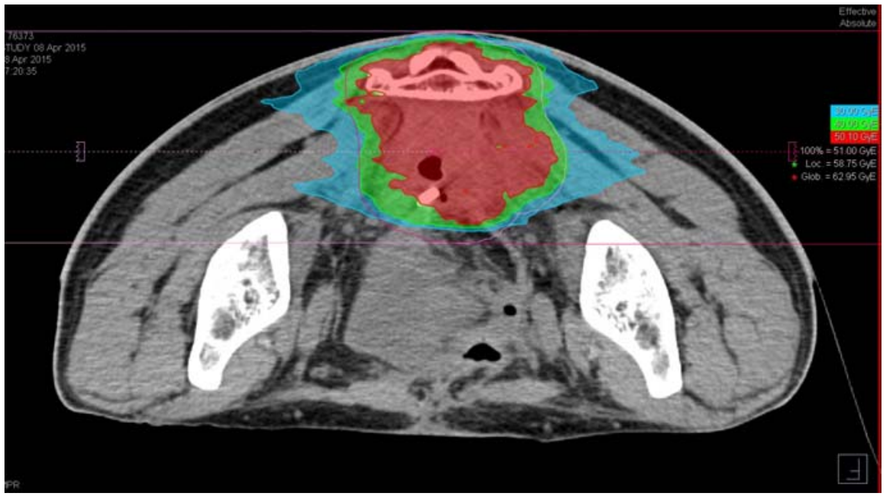
1 Year actuarial LC 82%

Toxicity: G2 – G3 0%

Re-treatments: 156 patients

NO OTHER THERAPEUTIC OPTION

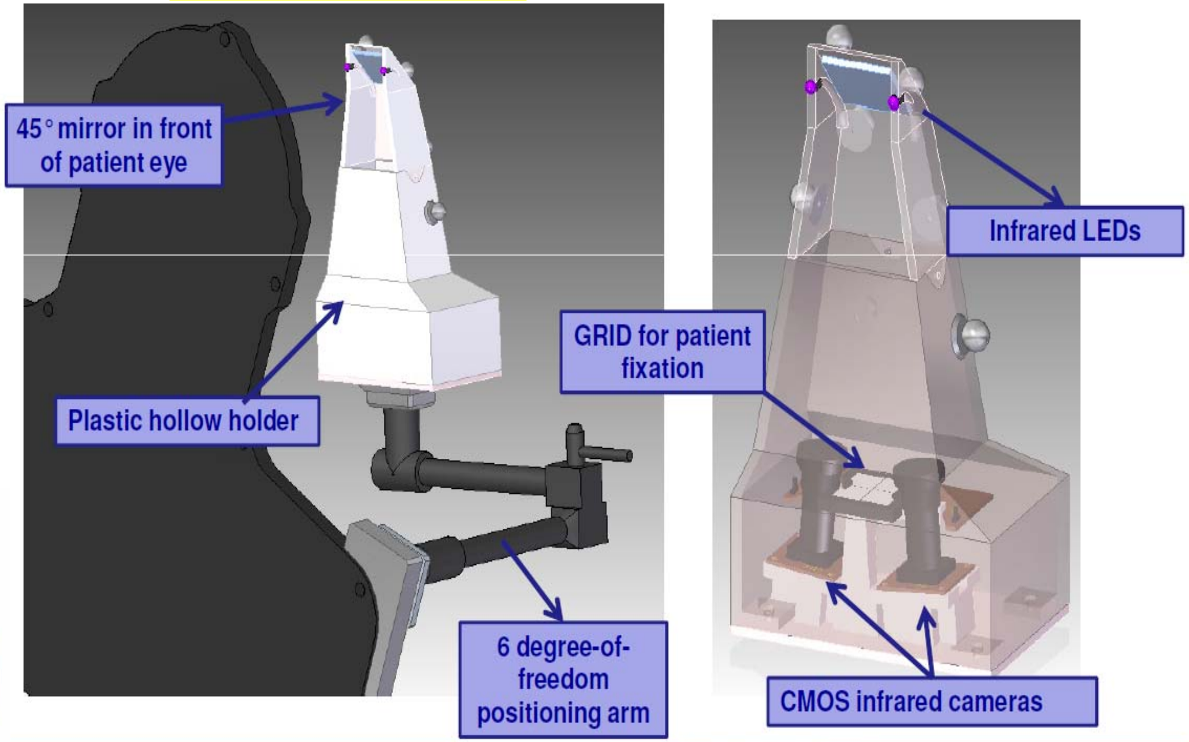


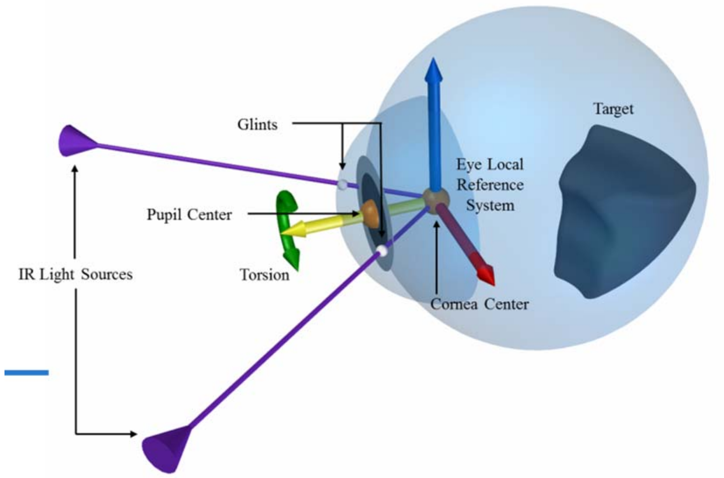


Eye melanoma

Non invasive eye tracking system for intraocular tumor localization in proton therapy treatment

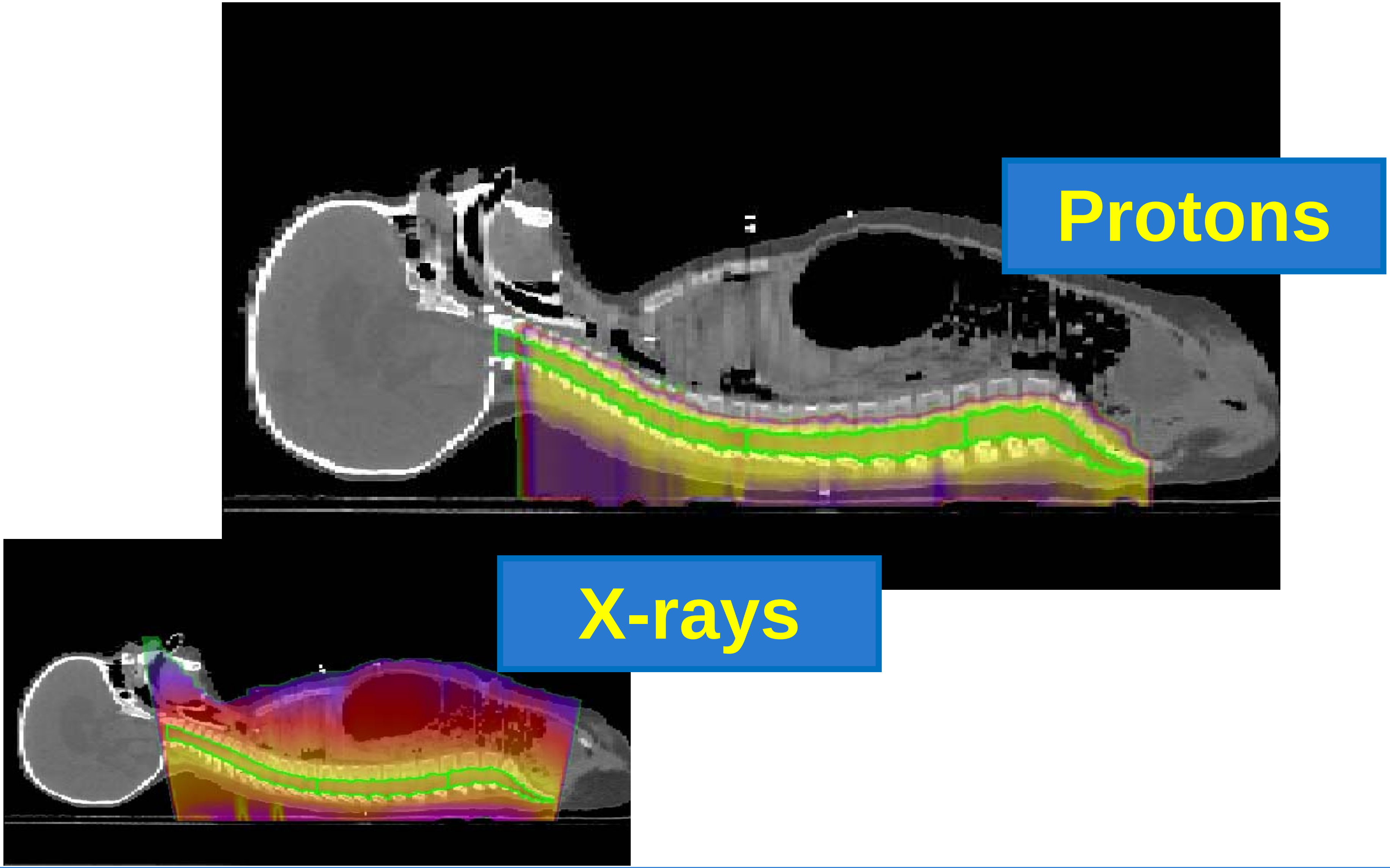
35 patients **60 GyE/ 4 fractions**



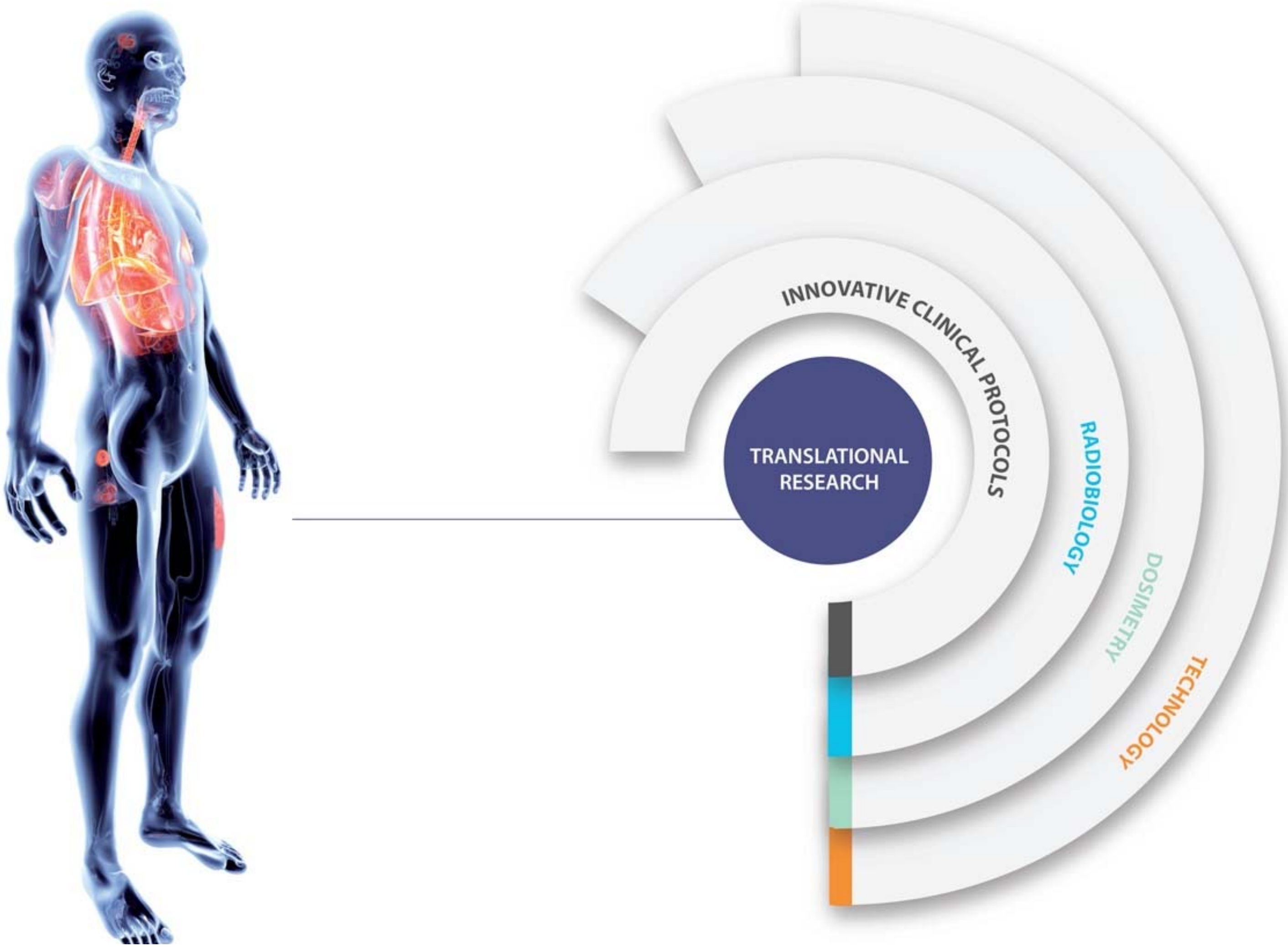


In collaboration with PoliMi INFN and UniPv

Pediatric patients: protons



Research is a must to keep CNAO up-to-date to stay always at the cutting edge



The Centre technology needs to evolve and adapt according to the research outcome: it is not a static "black box" producing beam, it is an evolving entity

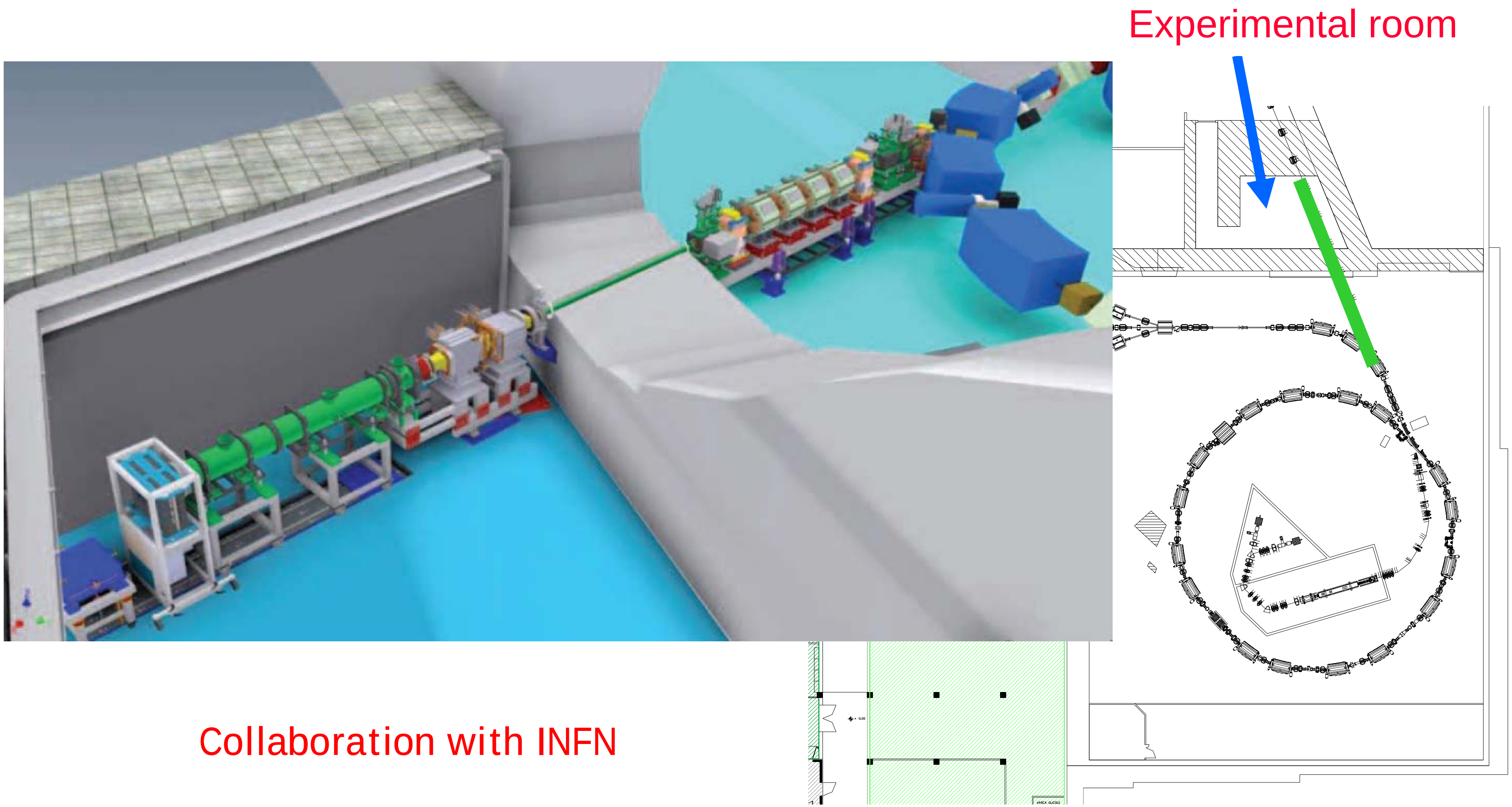
Research: hot topics

Beamtime for research projects in 2016

Ore	Gruppo	Ente	Nome esperimento	Descrizione esperimento
8	Calzolari, Bettega, Lafiandra	INFN-Mi		Irraggiamento cellule
8	Colautti, Chiriotti, Motisi	INFN-LNL, Uni Louvaine la Neuve (B)	Test di dosimetri TEPC	Test di rivelatore microdosimetrico (TEPC) di plastica tessuto-equivalente (2x2x5 mm3) Inserito in uno stelo di alluminio a sua volta inserito in un cubo di alluminio porta-elettronica
8	Antoccia, Berardinelli, DeVitis	Uni Roma3	Effetti Sostanze Radiosensibilizzanti	Irraggiamento di fiaschette di cellule
8	Tabocchini, Dini	INFN, ISS	Ethics	Irraggiamento cellule
8	Rosso, Camarlinghi, Collini, Sportelli, Zaccaro	INFN-Pi	RDH-DoPET	Test di rivelatori per sviluppo PET Online
8	Bisogni, Lodola, Marocchi,Piliero, Pirrone, Cerello, Pennazio, Fiorina	INFN-Pi / UniPi	INSIDE	Test di rivelatori per sviluppo PET Online
8	Tabocchini, Dini, Milazzo, Vulcano	INFN, ISS	Ethics	Irraggiamento cellule P
4	Dini, Milazzo, Vulcano, Manti, Perozziello, Boccia, Esposito	INFN-ISS, INFN-Na,	Ethics	Irraggiamento cellule P
8	Dini, Milazzo, Vulcano, Manti, Perozziello, Boccia, Esposito	INFN-ISS, INFN-Na	Ethics	Irraggiamento cellule P
8	Tamborini, Murtas, George	INFN-PV, CERN	GEMPIX in profondità	Test di un rivelatore GEMPIX chiuso in un case di PMMA e posizionato in fantoccio ad acqua.
8	Antoccia, Berardinelli	Uni Roma3	Effetti Sostanze Radiosensibilizzanti	Irraggiamento di cellule C
8	Rosso, Camarlinghi, Collini, Sportelli, Zaccaro	INFN-Pi	RDH-DoPET	Test di rivelatori per sviluppo PET Online
1	Villani, Zhige	Rutherford Appleton Lab, UK	CMOS Sensor Validation	Irraggiamento di un sensore e confronto con nostra camera a ionizzazione

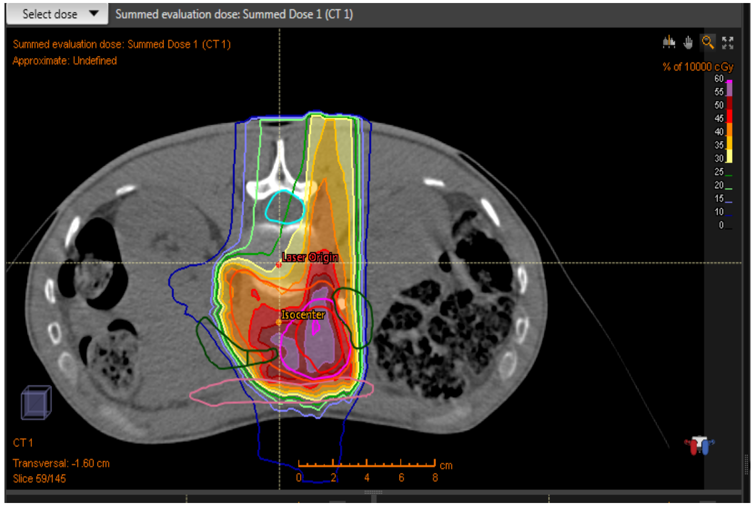
150 h

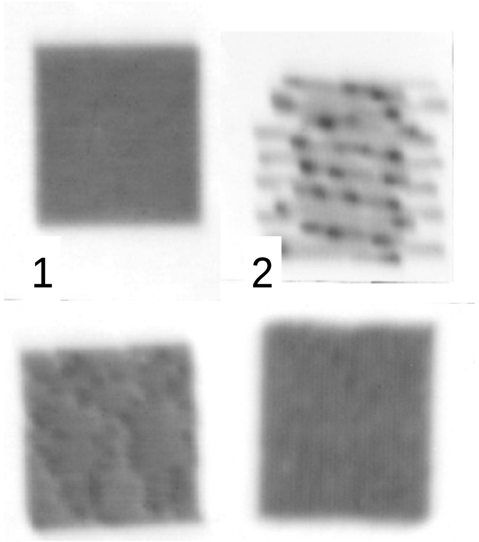
At CNAO a 5th beamline devoted to research is presently under construction



Collaboration with INFN

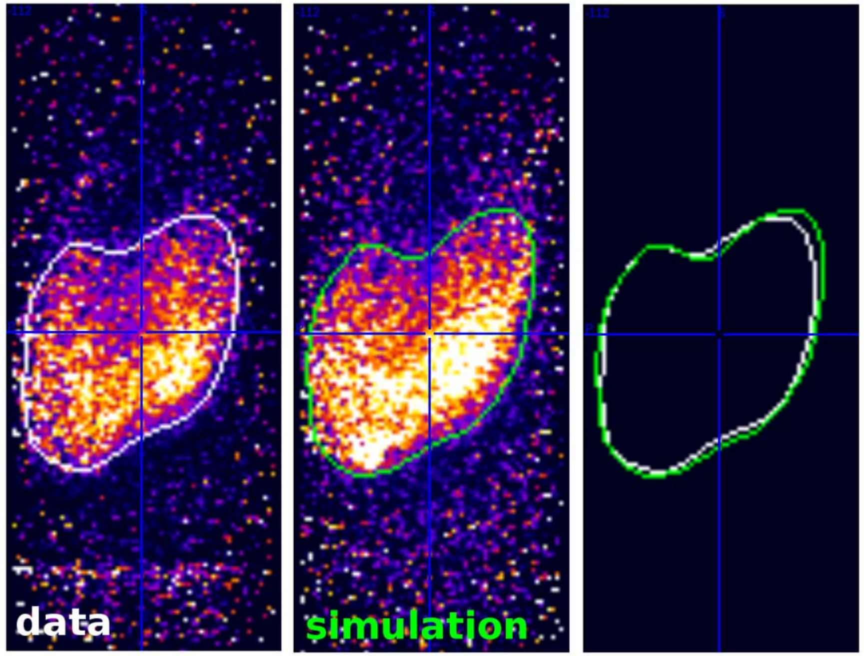
CNAO is treating moving organs with carbon ions: active scanning+gating+rescanning

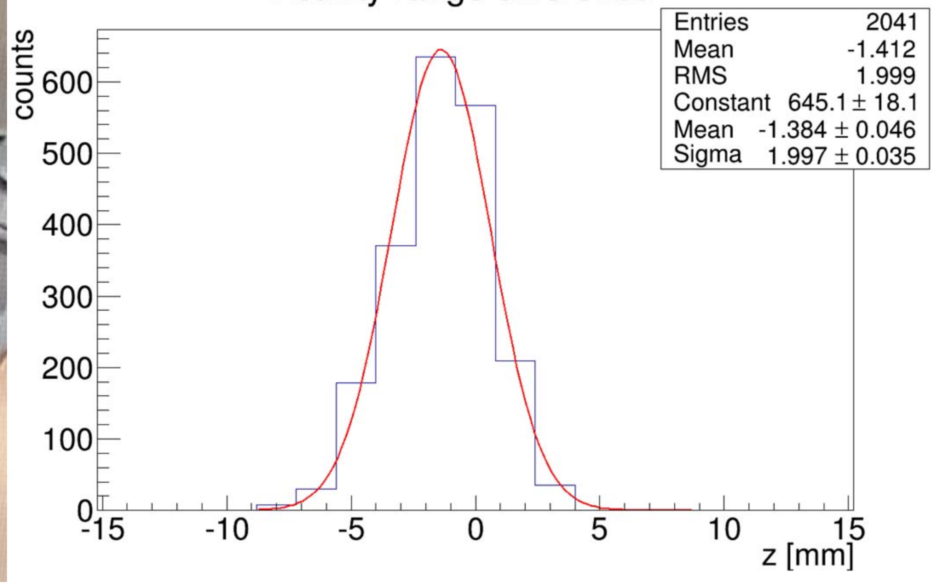




Goal: tumour tracking in real time

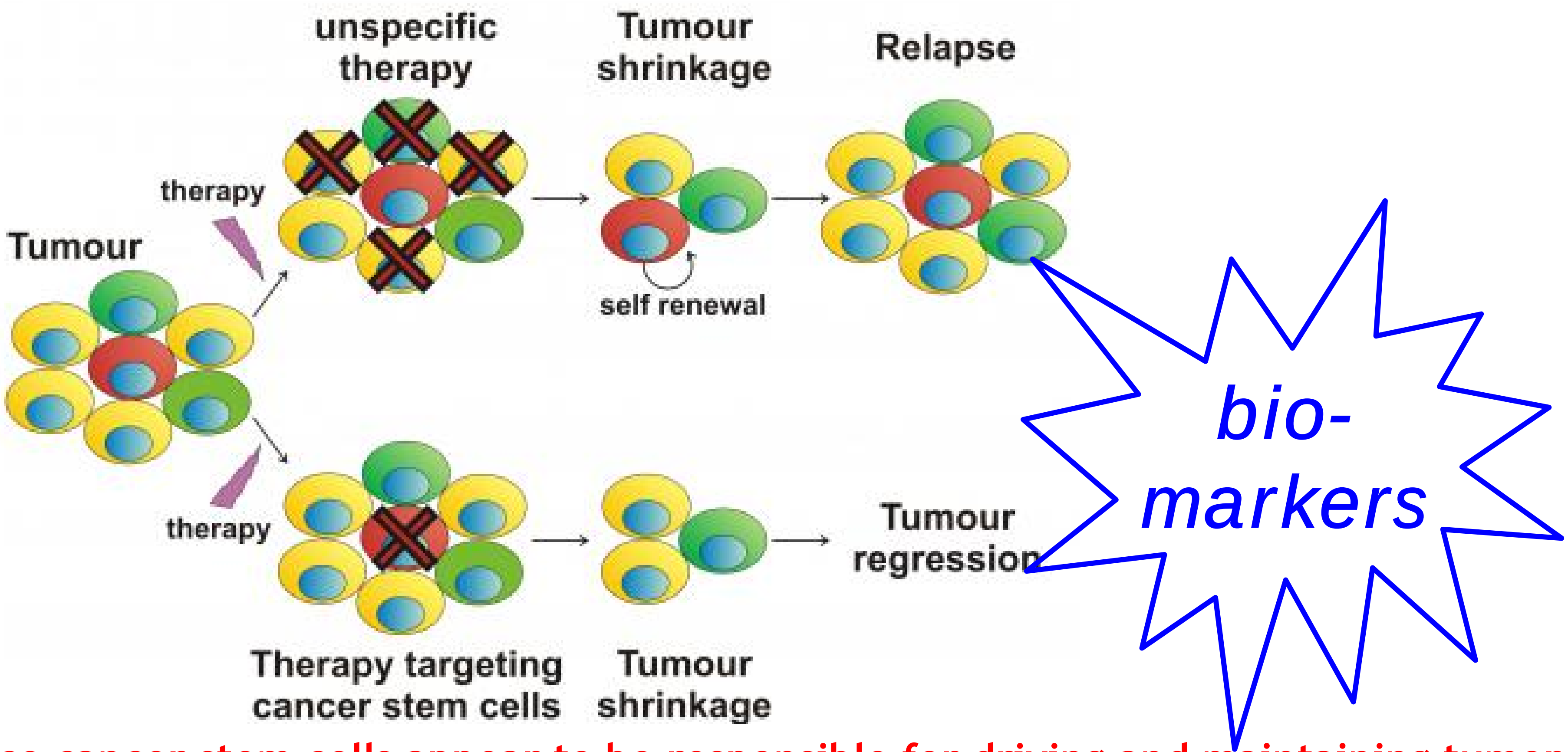
Patient - 01/12/2016
Proton beam
4 min treatment + 1min after





Radiobiology: Cancer stem cells

"A small subset of cancer cells within the tumor mass, which constitutes a reservoir of self-sustaining cells with exclusive ability of self-renewal and tumor maintenance" *(from the Cancer Stem Cell Workshop of the American Association for Cancer Research in 2006)*



Since cancer stem cells appear to be responsible for driving and maintaining tumor growth in many tumors, it is critical to understand the mechanisms by which these cells resist commonly used therapies such as chemotherapy and radiotherapy

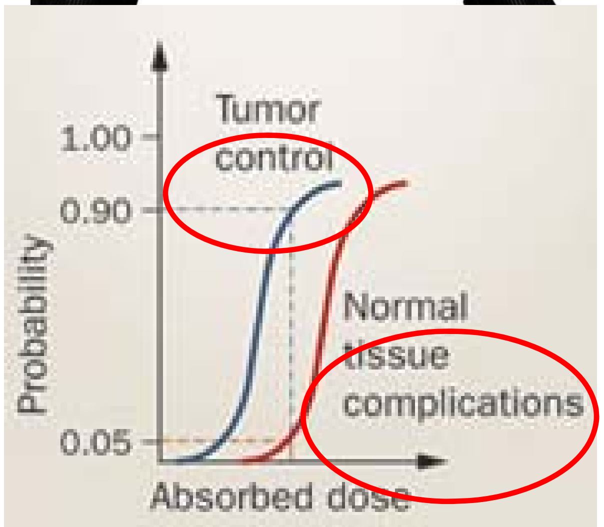
Combined treatments

Particles + radiosensitizers = ???

Particles + chemotherapics = ???

Particles + photons = ???

Particles + …..= ???



Although heavy-ion therapy has provided favorable clinical outcome with irradiation alone, the suitability of particle beam irradiation for combination with other therapeutic modalities such as chemotherapy, endocrine therapy, low LET radiation ("boost protocols") and biological therapies warrants extensive studies, in the context of both enhancing tumor control and reducing normal tissue complications.

Thank you

“Real progress happens only when advantages of a new technology become available to everybody”

H. Ford

fondazione CNAO

Centro Nazionale di Adroterapia Oncologica