HADRONTHERAPY:
exploring new challenges against cancer

Sandro Rossi

International Symposium “Passion for Science”: facing global challenges
Varenna, June 20-21, 2022

CNAO
Centro Nazionale di Adroterapia Oncologica

Objectives and Outline

Objectives:

- ✓ Passion for science: hadrons, from basic physics to society/patients
- ✓ Facing global challenges: new technologies to reduce costs, spread hadrontherapy, improve efficiency and outcome

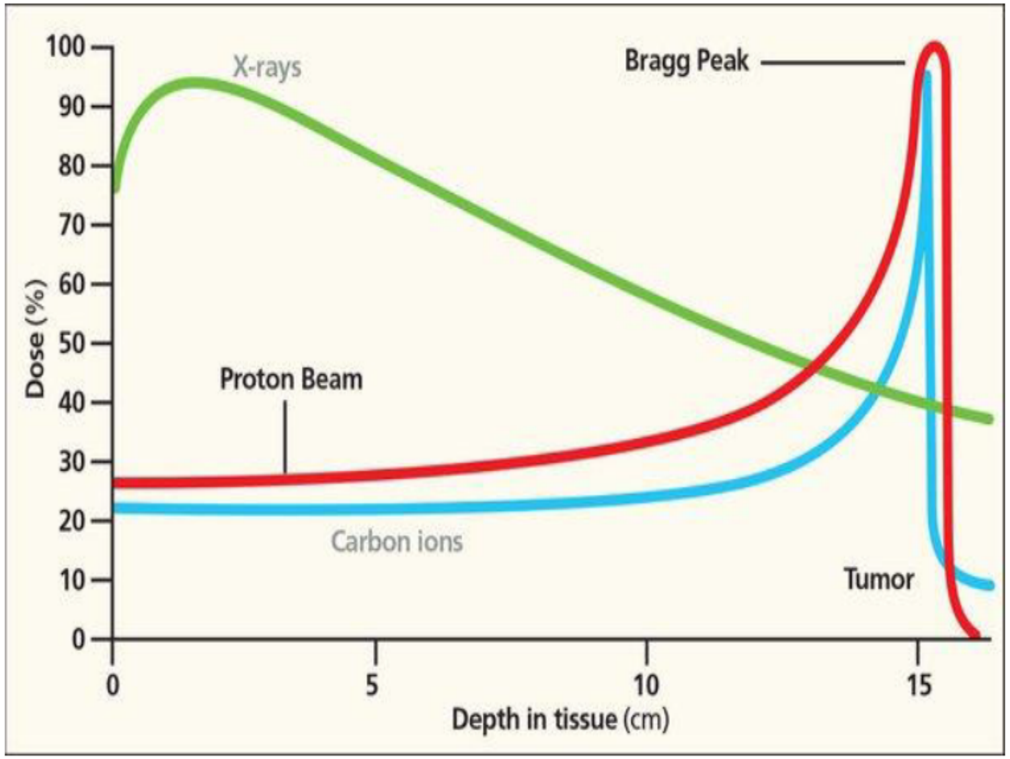
Outline:

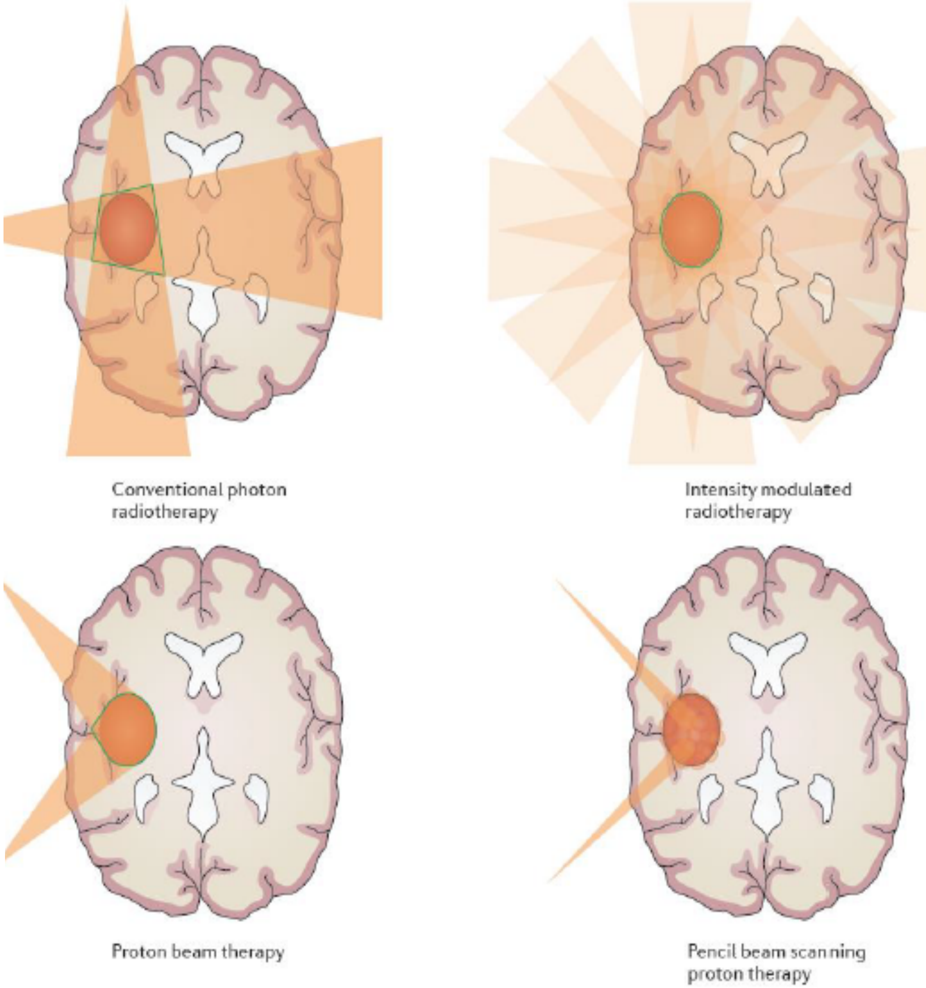
- ✓ Technologies applied to hadrontherapy
- ✓ Clinical results and future developments
- ✓ Optimization of patient treatments
- ✓ Concluding remarks

Almost 15.000 MV therapy machine in 160 Countries, 7.800 centres

Radiotherapy: 40-60% of cancer patients benefit of radiotherapy [IAEA]

Particles: PRECISION to treat ‘difficult’ cases





X

dosimetric benefit

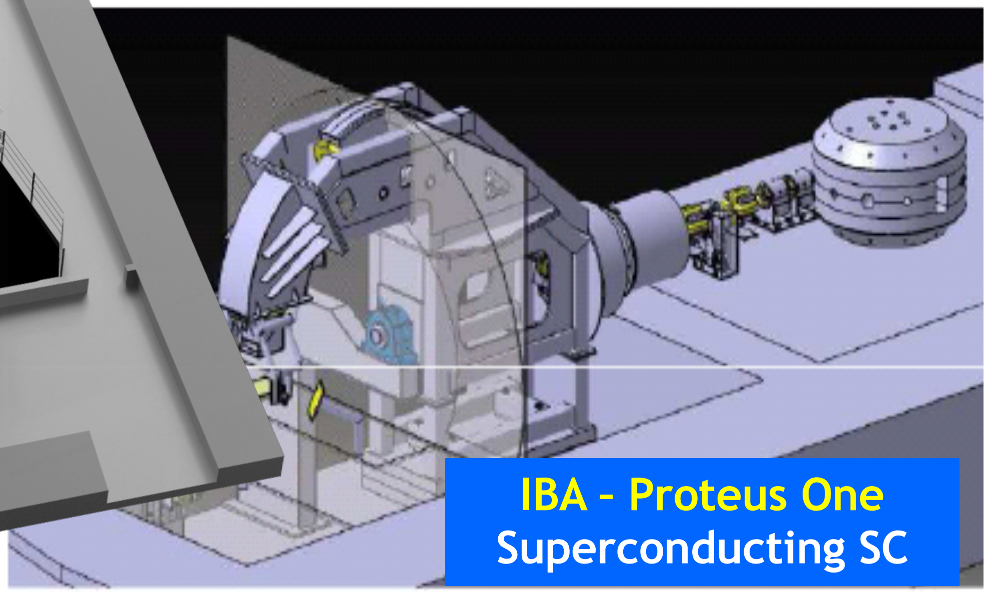
conditio sine qua non

clinical benefit

X ?

96 centres with protontherapy (+30 in construction)

330.000 patients treated (+40.000/year) [www.ptcog.ch]



13 centres carbon ions, 6 multi-particle (+5 in construction)

45.000 patients treated (+5.000/year) [www.ptcog.ch]

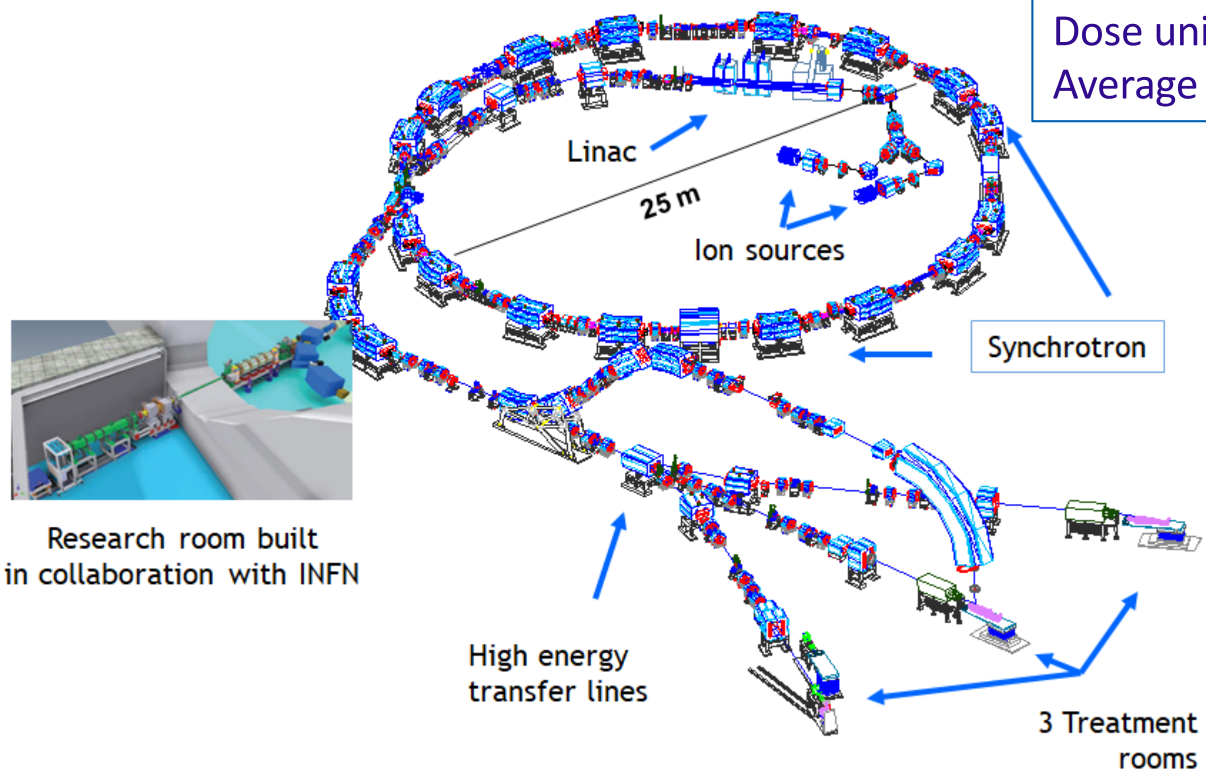
Accelerator for hadrons are circular

cyclotrons and synchrotrons (only choice for carbon)

Accelerated ion	p, C
Energy range (MeV/u)	60-225 (p) (30-320mm)
	120-400 (C) (30-270mm)

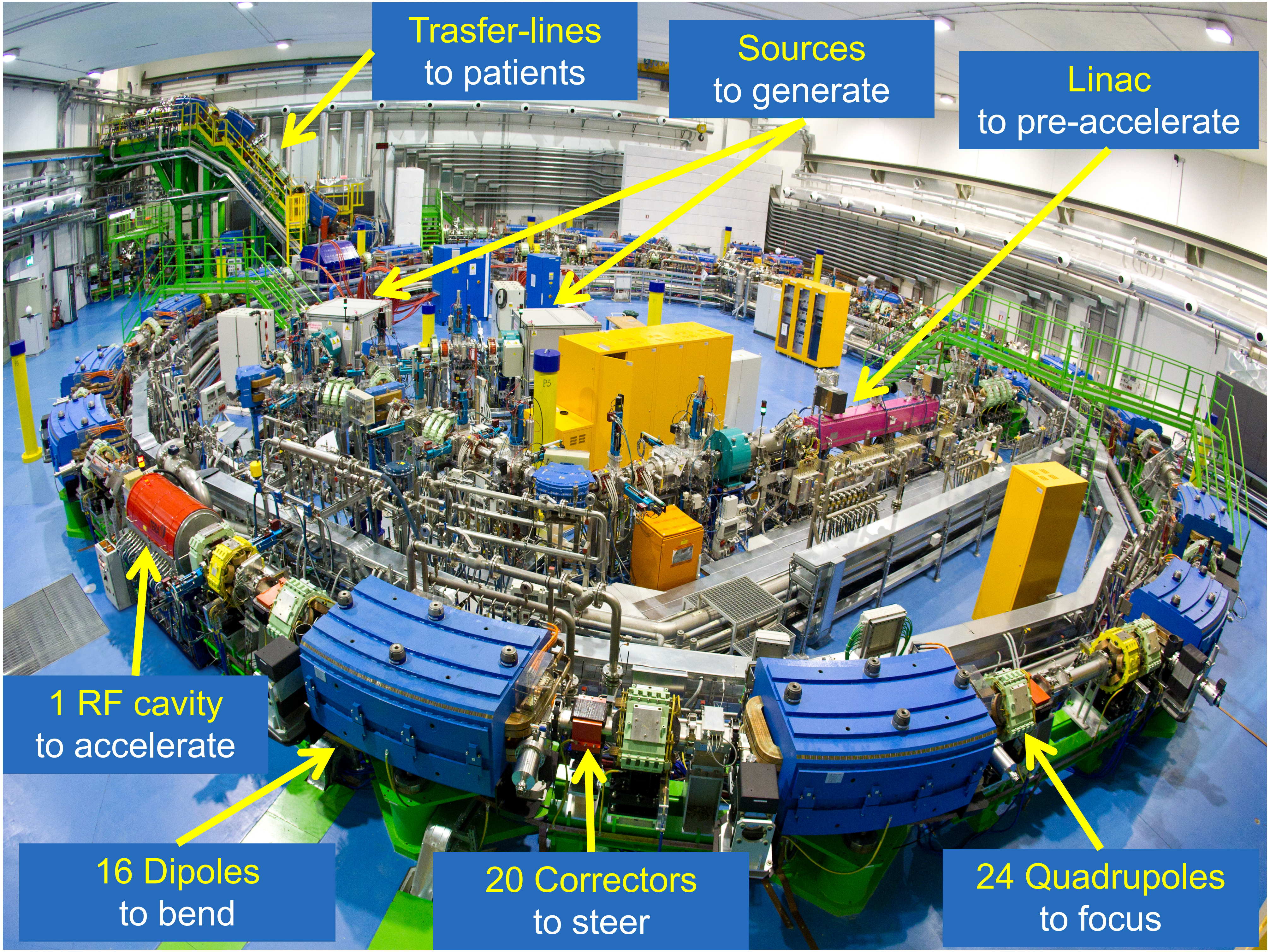
The CNAO synchroton has a compact design

Extraction	Slow
Dose uniformity	± 2.5%
Average dose rate	2 Gy/min/liter



Field size (mm × mm)	200 × 200
Beam size (FWHM) (mm)	4-10
Beam position precision (mm)	0.1

Intellectual property shared by CNAO - INFN - CERN


Trasfer-lines
to patients
Sources
to generate
Linac
to pre-accelerate
1 RF cavity
to accelerate
16 Dipoles
to bend
20 Correctors
to steer
24 Quadrupoles
to focus

Imaging and positioning

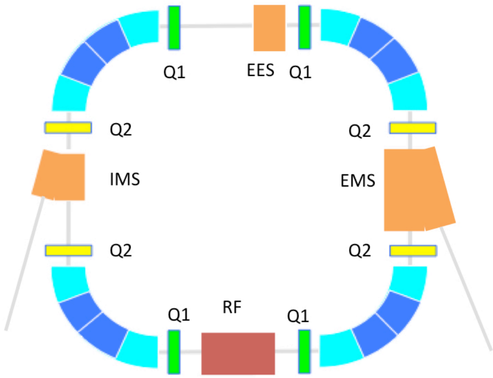
A world of science/technology to master the treatment

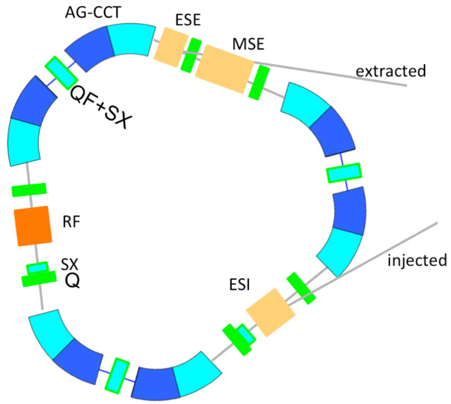
- ✓ Off-line imaging to “define target and OARs”
- ✓ Automated patient positioning systems
- ✓ In-room imaging devices for inter/intra-fractional uncertainties detection and compensation (new NMR devices)
- ✓ Management of moving organs (breathing synch./rescanning)

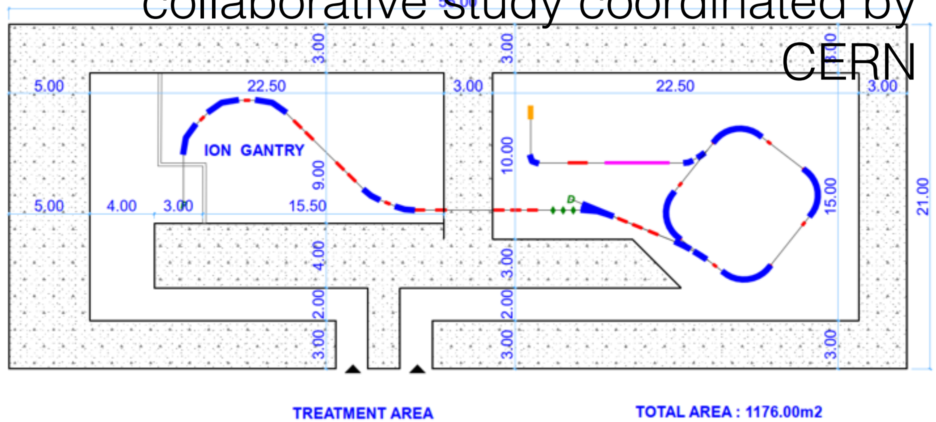
Heavy Ion Therapy Research Integration

Next Ion Medical Machine Study (NIMMS)

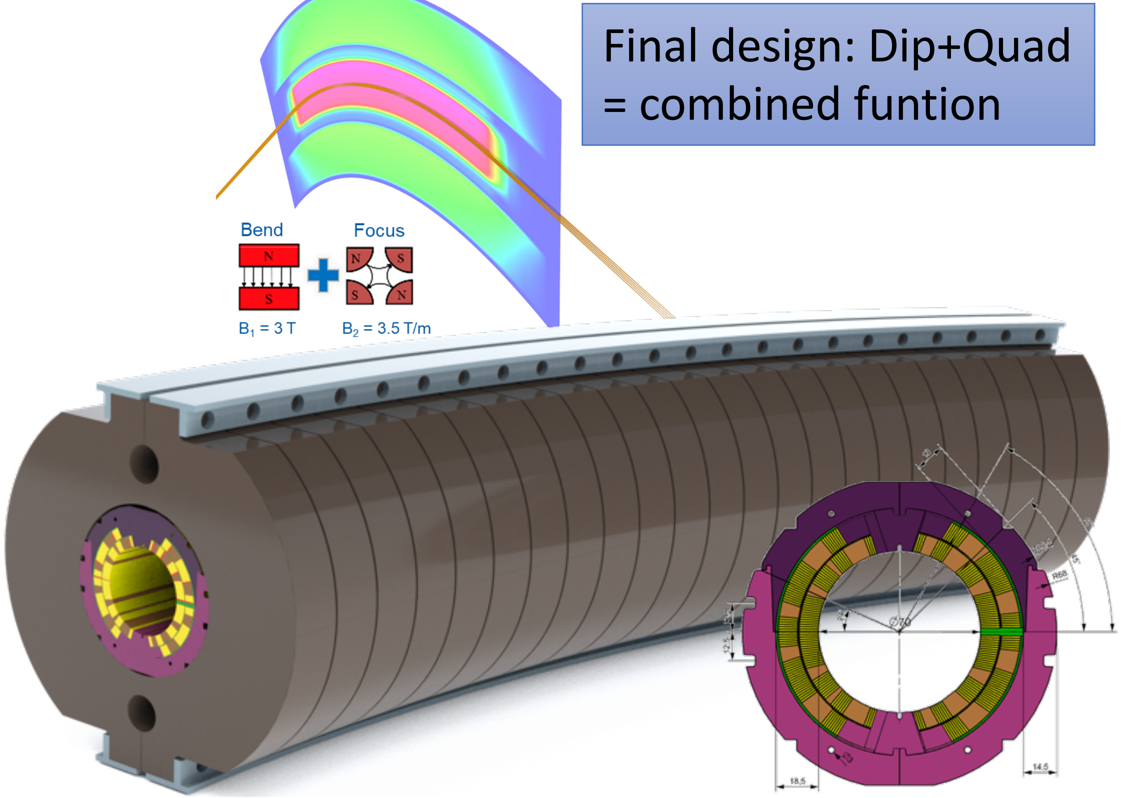
collaborative study coordinated by CERN







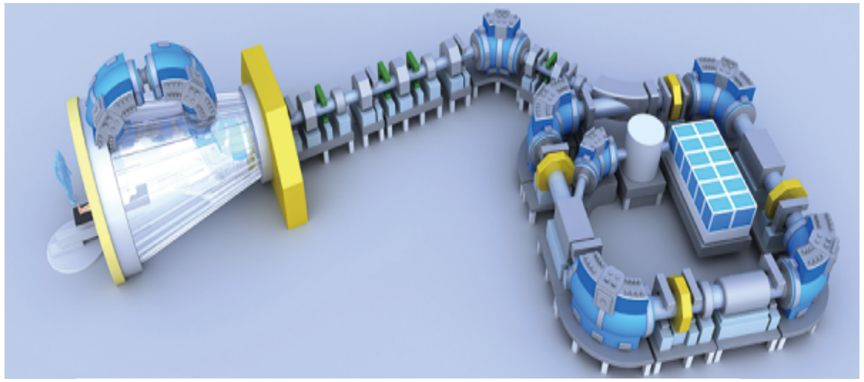
Superconducting Magnet Design



Final design: Dip+Quad = combined funtion

Quantum Scalpel

5th Model (10x20 m²)



Creation of Harmonious Diversity

QST National Institutes for Quantum Science and Technology

R&D: carbon ions gantry

Collaboration CNAO-INFN-CERN-MedAustron

Signed 31 March 22, 4 years project

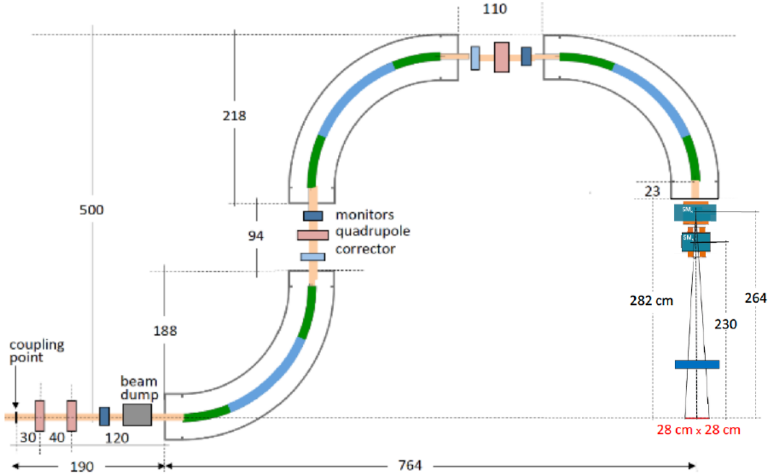


Figure 1. *Layout of the gantry and the scanning system based on 90° canted cosine theta magnets running at 4 T.*

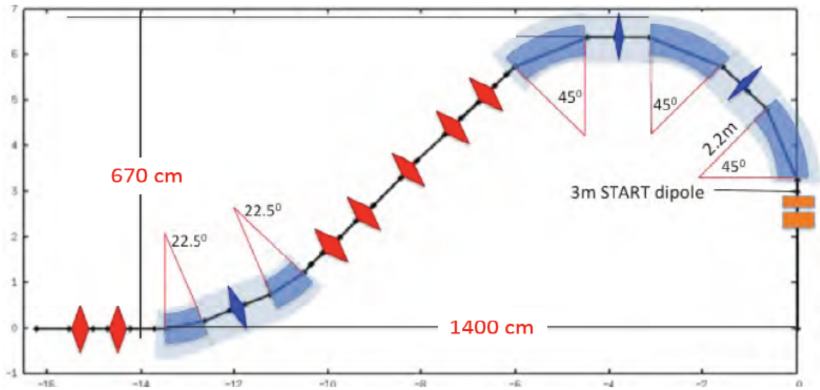
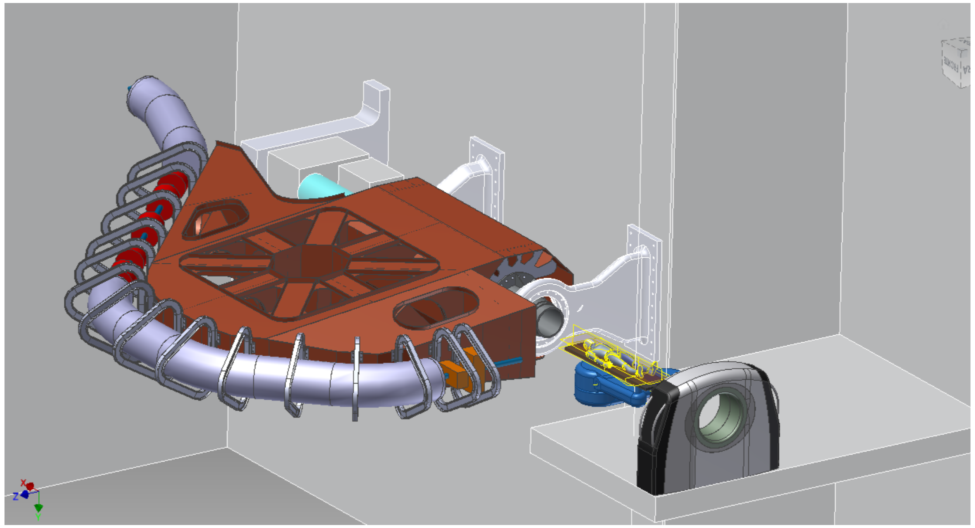


Figure 3. *In this design the 22.5° and 45° cosine theta magnets run at 3 T. The 140 cm needed for the quadrupole between the last two magnets contribute 1 m to the gantry radius.*



1951 2021 infn

70 ANNI DI RICERCA DISEGNANDO IL FUTURO

Superconducting Ion Gantry

CSN5 – Call 2021

SIG

Superconducting Ion Gantry

Lucio Rossi

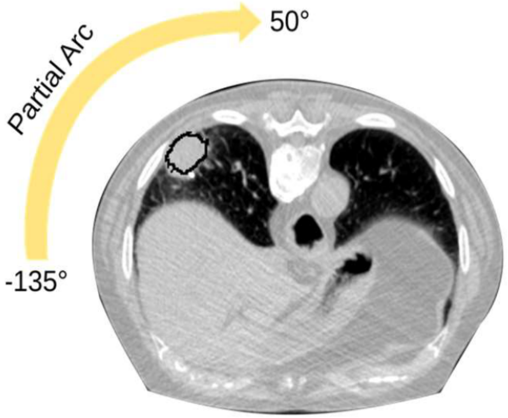
Università di Milano e sezione INFN di Milano – LASA

R. Musenich INFN-GE, L. Sabbatini LNF, S. Giordanengo e E. Fiorina INFN-TO

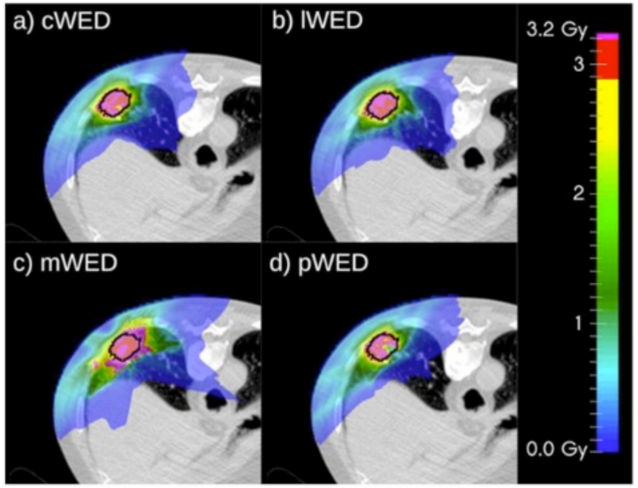
SIGRUM

Superconducting Ion Gantry with Riboni's Unconventional Mechanics

Aternative solutions for patient treatments



Arc - Therapy

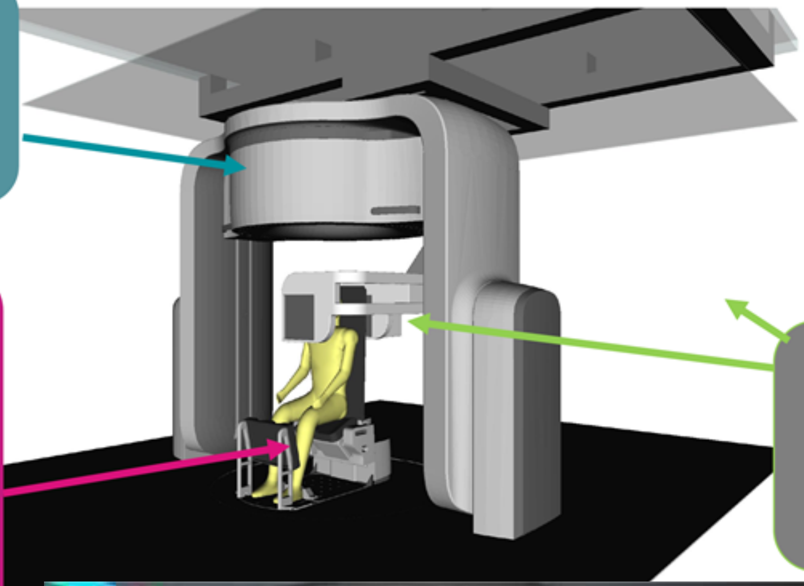


A Dual-Energy CT Capable Of Imaging

CT Anywhere Above the Upper Thigh

An Upright Positioning System Capable Of Treating

Intracranial
Head & Neck
Breast & Lung
Prostate



LEO Cancer Care

P-Rad Panels for

- *Proton Radiography*
- *Proton CT*
- *System QA*
- *Patient specific QA*

P-Rad System

Front detector
Back detector + Delta – E detector

Mechanical insertion Arm

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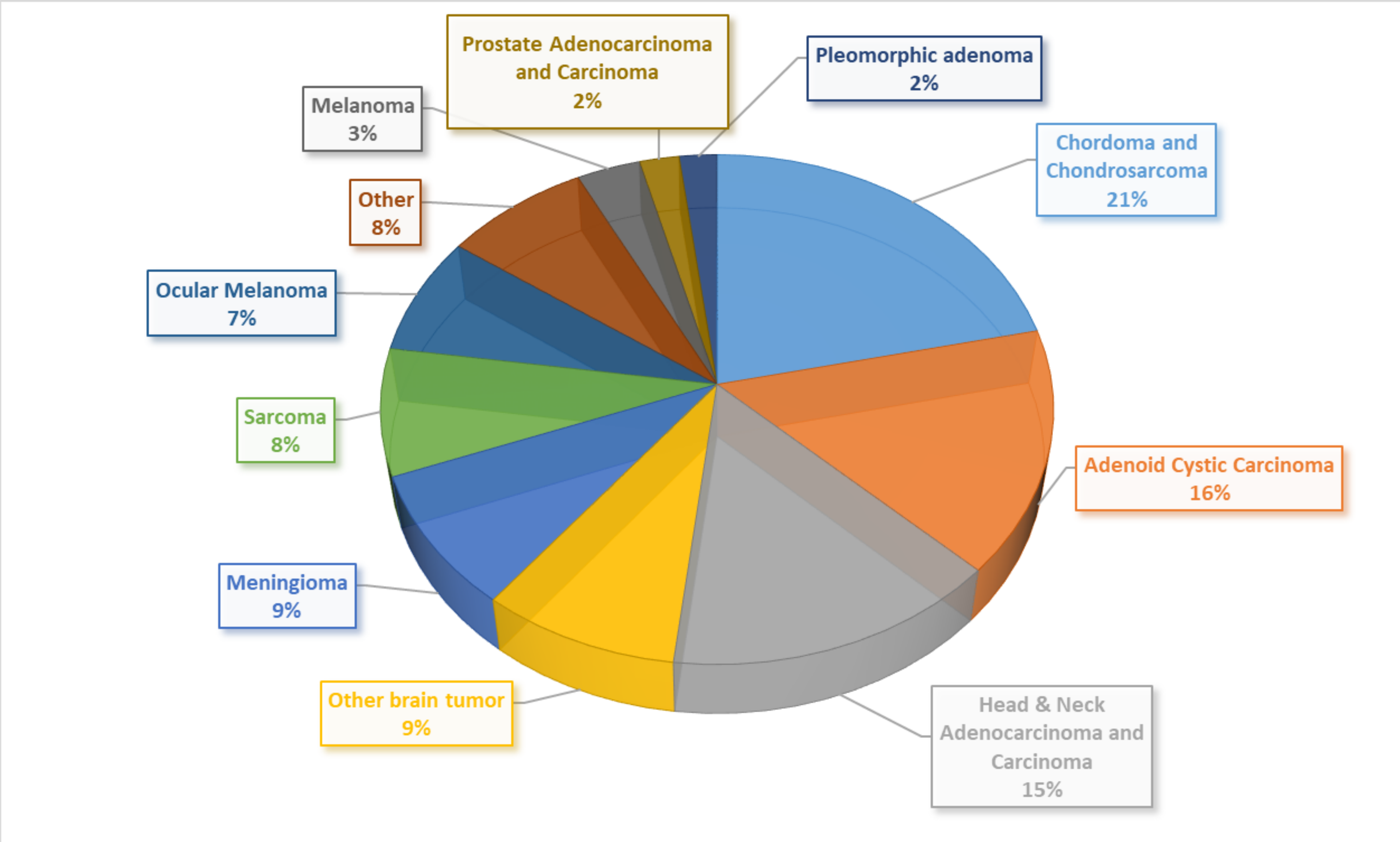
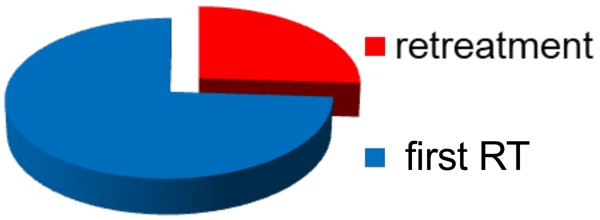
CNAO: 4000 patients

54% carbon ions- 46% protons

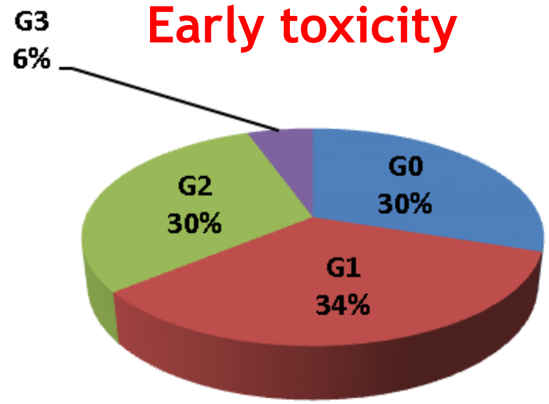


Treatments: efficacy + reduced toxicity

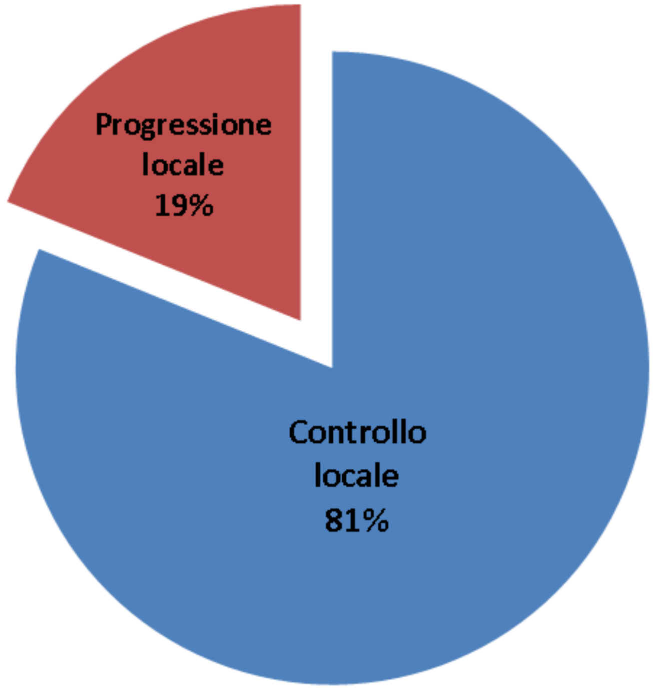
26% re-treatment



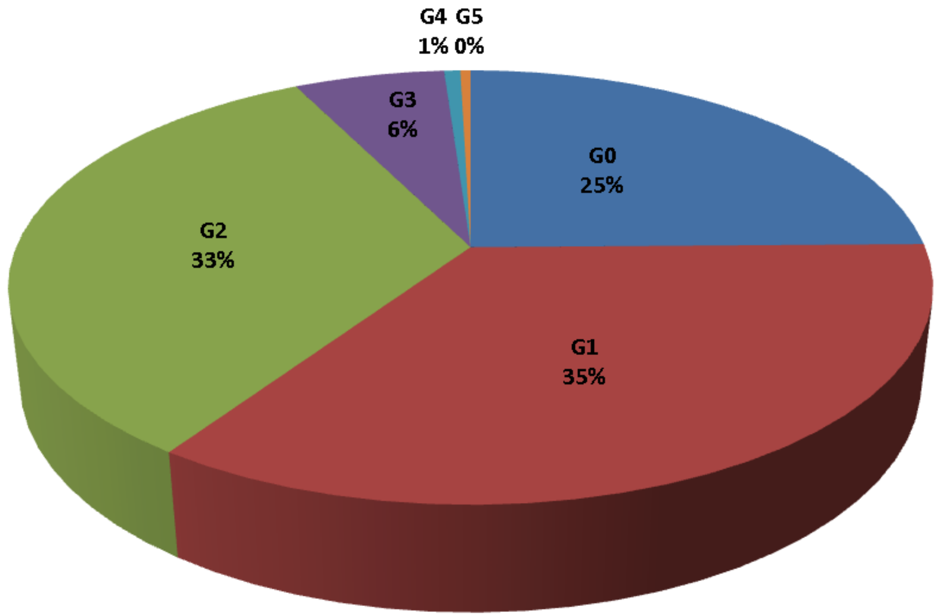
Early toxicity



Undistinguished local control



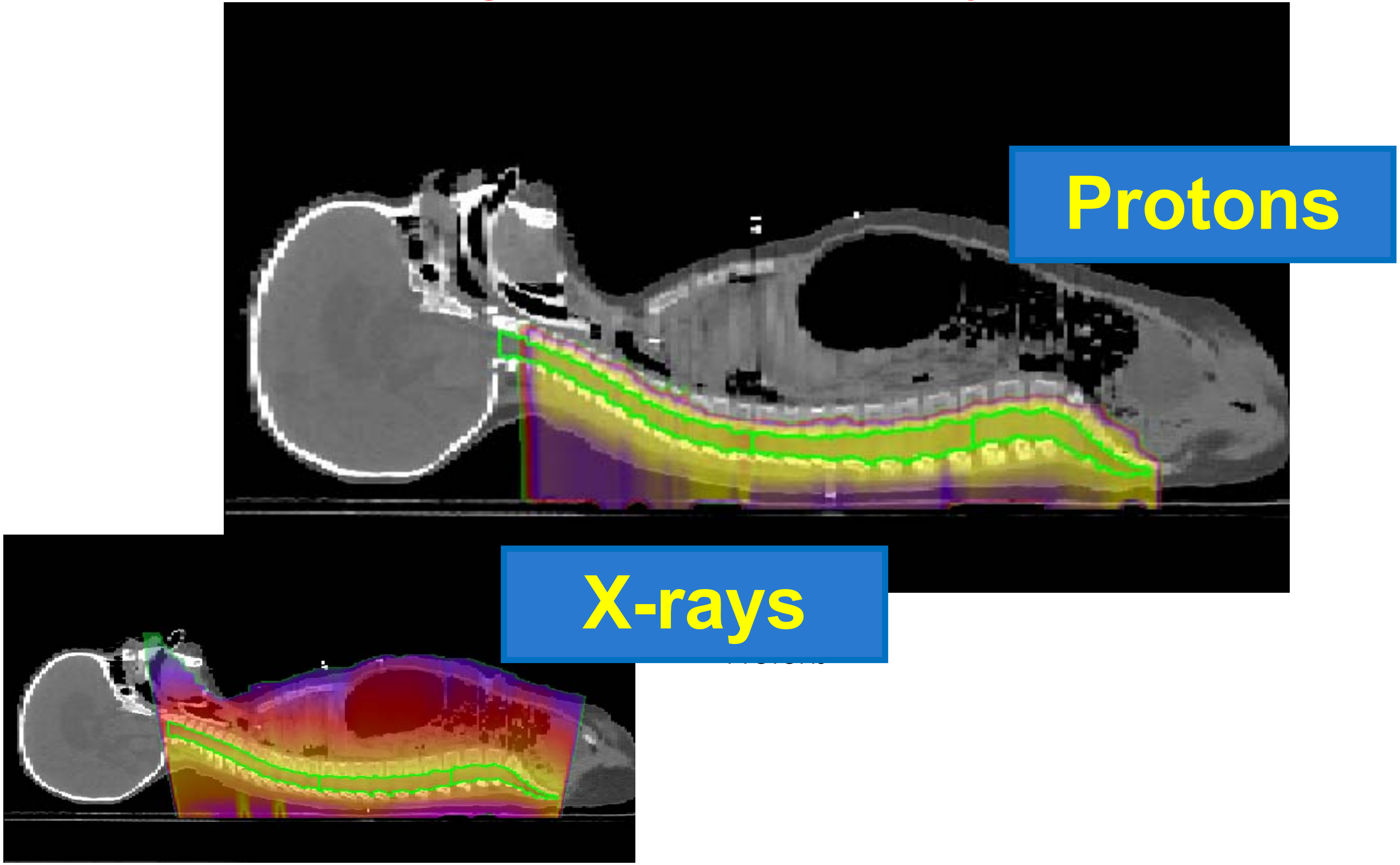
Late toxicity



Clinical Dept. 2021: 50 publications, mean IF 5.810

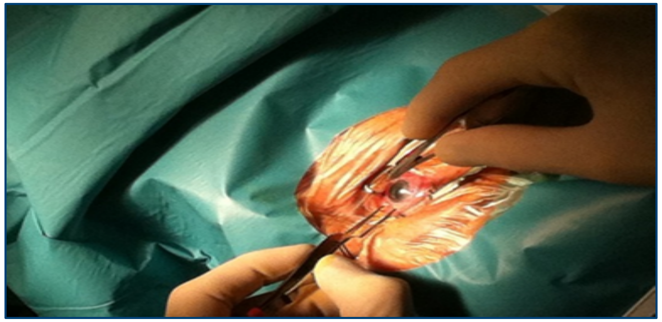
Pediatric patients elective for protons

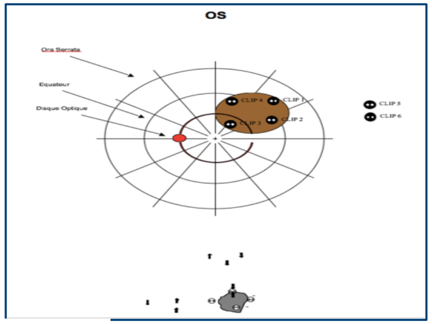
Less dose to healthy tissues
to reduce long term risks of secondary tumours



Ocular melanoma: small volumes

INT – Milan + Galliera – Genova:
patient selection and tantalium clips



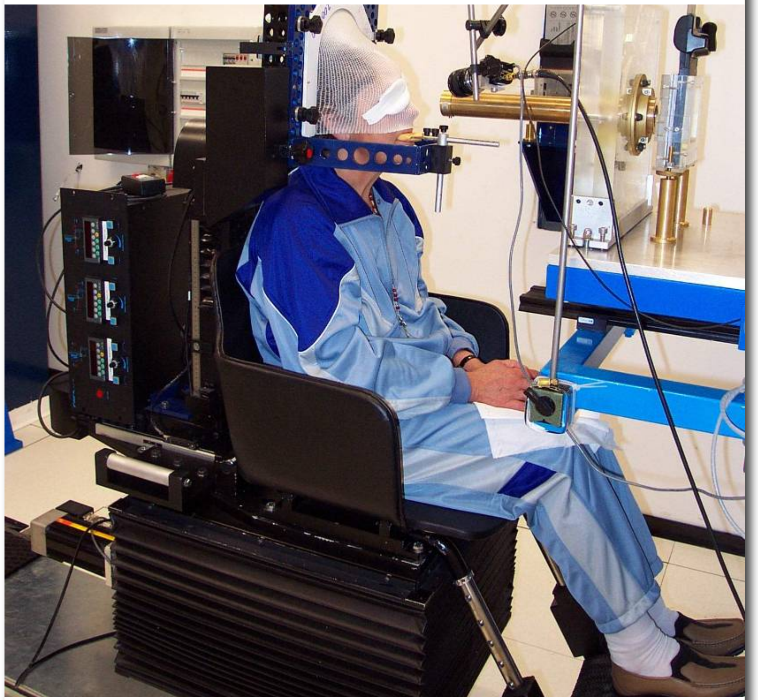


> 200 patients

Protons: 60 GyE (4 fx)

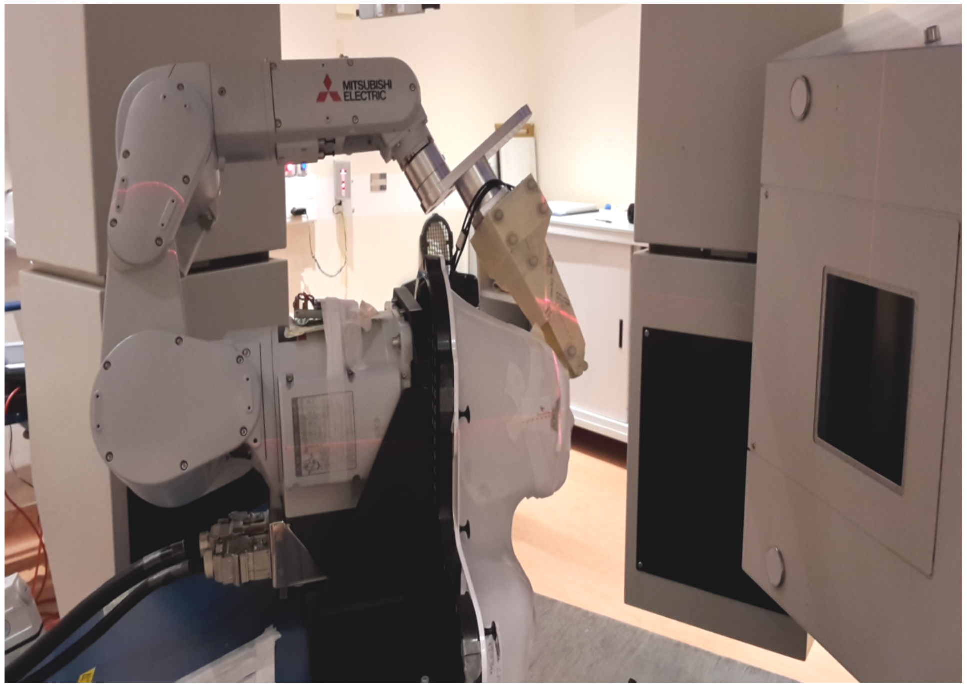
Local Control >95%
Eye preservation >90%
Visual function >45%

CATANA project (INFN-LNS)



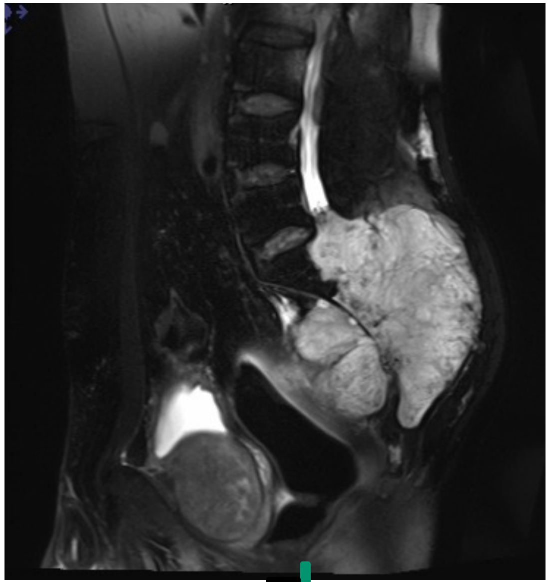
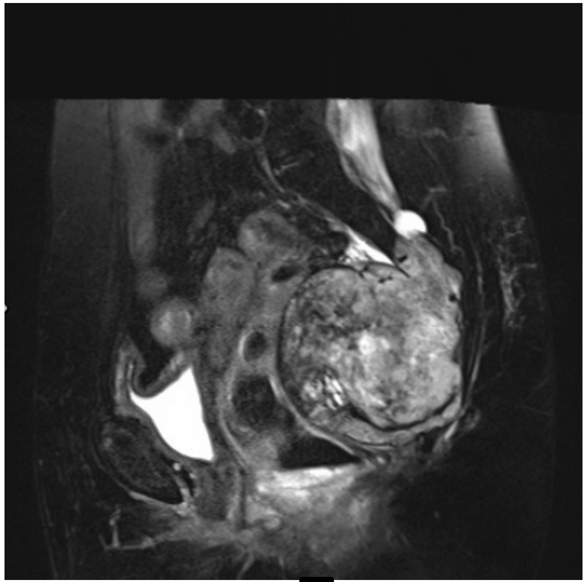
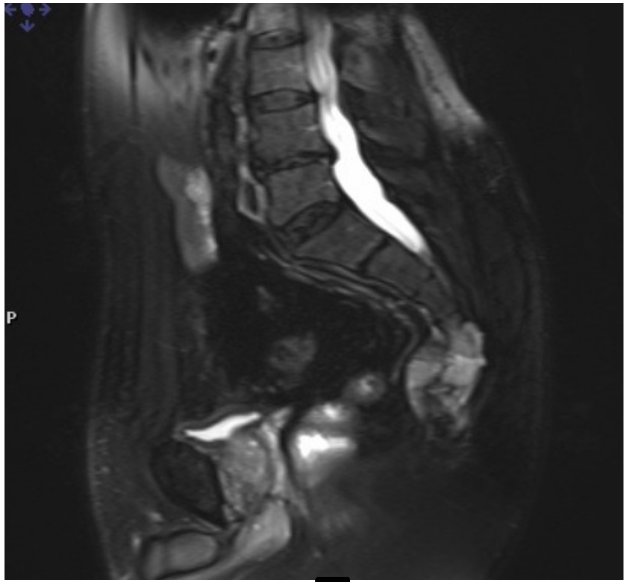
350 patients treated

Collaboration with Politecnico Milano

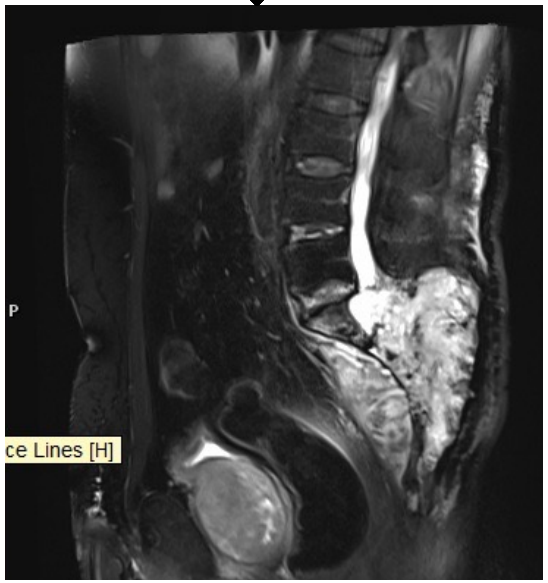


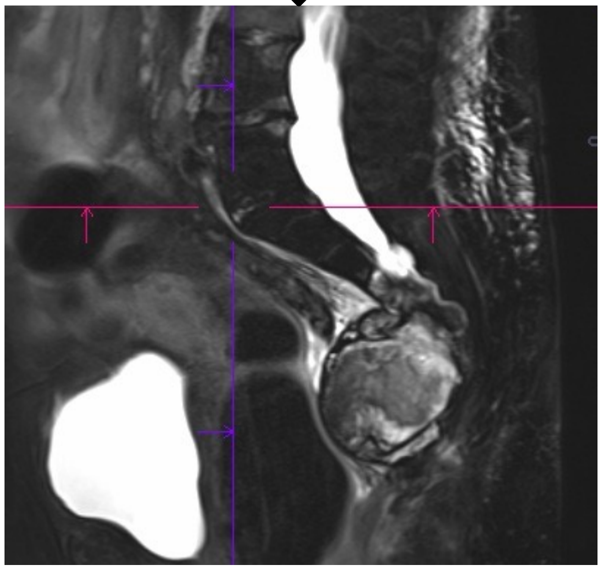
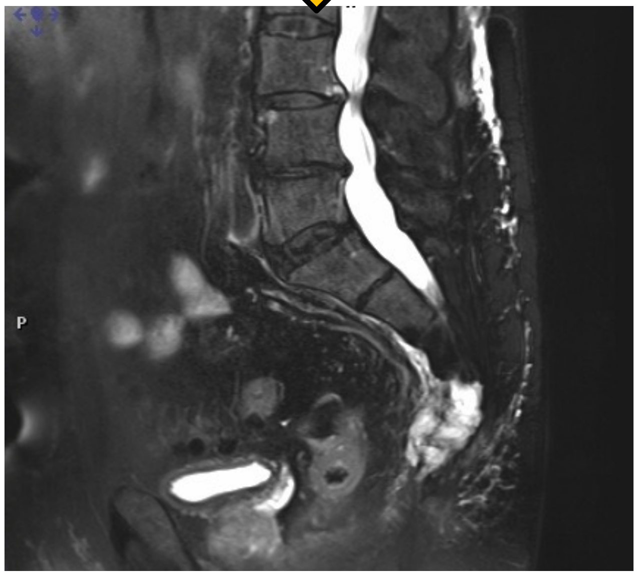
Sacral Chordoma: big volumes

CIRT 74 GyE
16 fractions IMPT

After 1 year



Essential Levels of Assistance (LEA)

1. Chordoma & chondrosarcoma base/spine
2. Meningiomas
3. Brain tumors (trunk)
4. ACC Salivary Glands
5. Orbit tumors including eye melanoma
6. Sinonasal carcinoma
7. Soft Tissue & bone Sarcoma (every sites)
8. Recurrent tumors (retreatment)
9. Patients with immulogical desorders
10. Pediatric solid tumors

11. Tumors for which hadrontherapy guarantees a better dose distribution wrt the best alternative providing a 10% better result in terms of NTCP or TCP

In Italy (60 million inhabitants) estimated cases 1-10:

Protons: about 5.000 patients/year

Carbons: about 1.000 patients/year

Non oncological application: ventricular arrhythmia

(Collaboration with San Matteo Hospital, Pavia)

Published on:
European Journal of Heart Failure

PubMed.gov

Search PubMed

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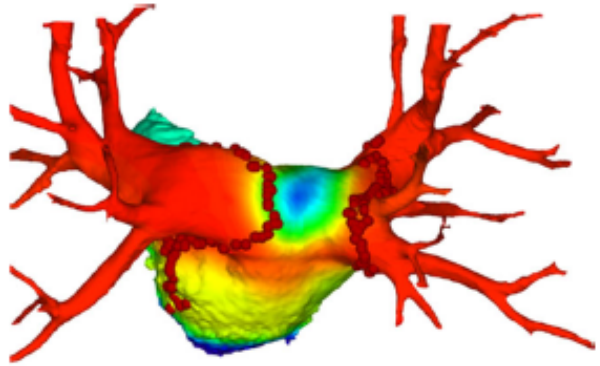
› Eur J Heart Fail. 2020 Nov 12. doi: 10.1002/ejhf.2056. Online ahead of print.

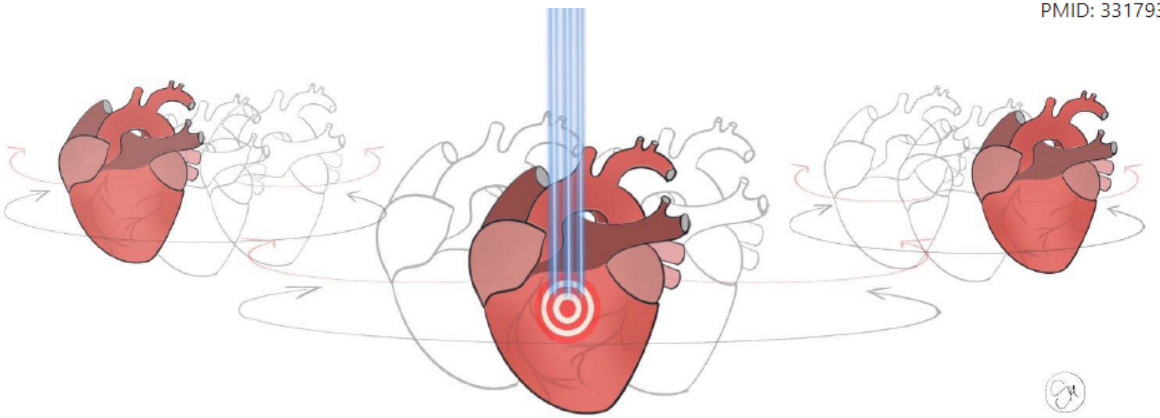
The First-in-Man Case of Non-invasive Proton Radiotherapy to Treat Refractory Ventricular Tachycardia in Advanced Heart Failure

Veronica Dusi [1 2], Viviana Vitolo [3], Laura Frigerio [1 4], Rossana Totaro [1 4], Adele Valentini [5], Amelia Barcellini [3], Alfredo Mirandola [3], Giovanni Battista Perego [6], Michela Coccia [2], Alessandra Greco [4], Stefano Ghio [4], Francesca Valvo [3], Gaetano Maria De Ferrari [7], Massimiliano Gnecchi [1 2], Luigi Oltrona Visconti [4], Roberto Rordorf [1 4]

Affiliations + expand

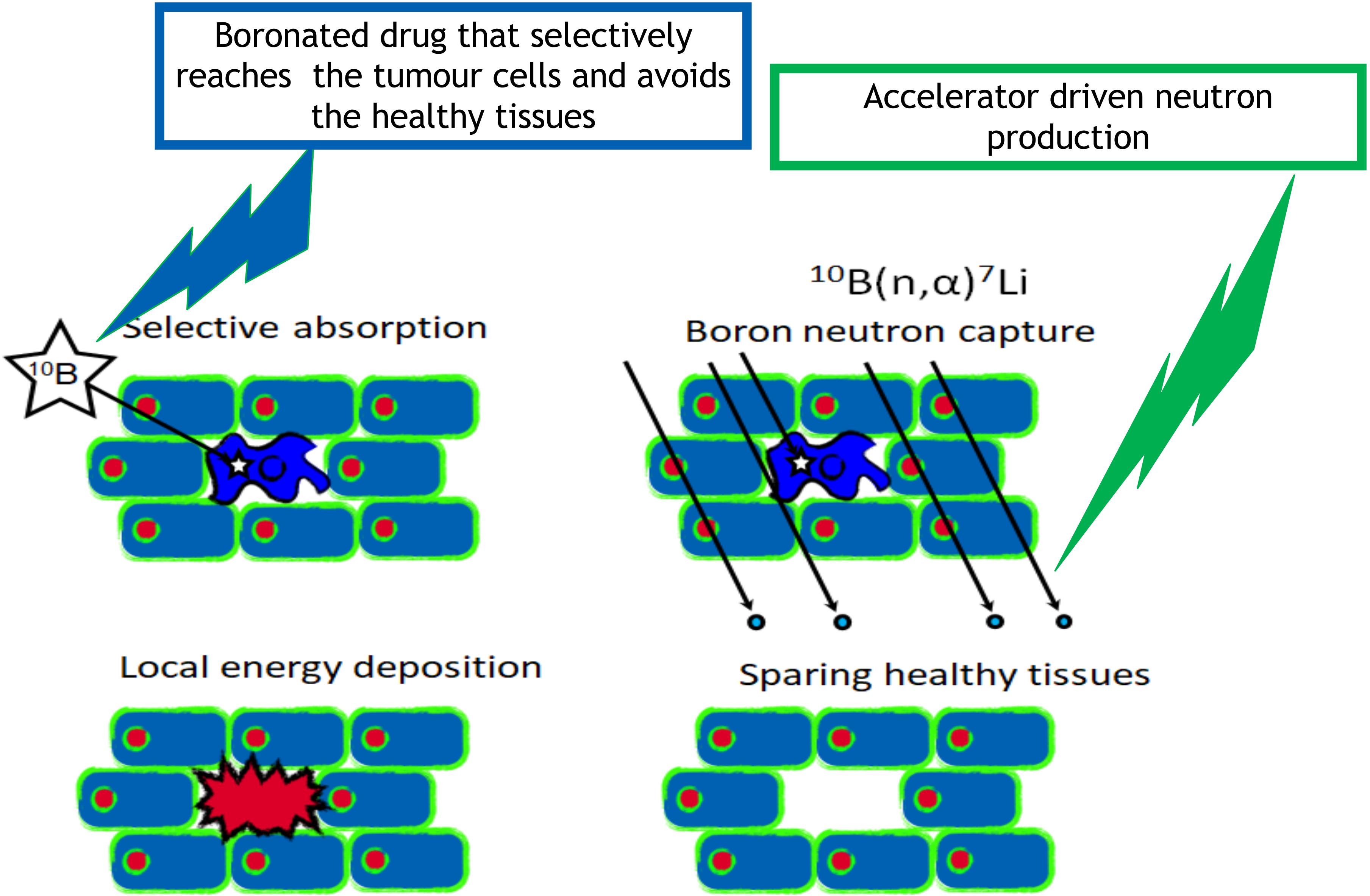
PMID: 33179329 DOI: 10.1002/ejhf.2056





BNCT: Boron Neutron Capture Therapy

2-steps research approach for metastasized tumours



BNCT: proton tandem accelerator

Collaboration agreement CNAO+TLS
signed November 2020

Start installation at CNAO: end 2023

Proton energy 2.5 MeV
Intensity 10-15 mA
p-Li reaction

alpha α beam™

tae LIFE SCIENCES

White Book

BNCT@CNAO

CNAO-INFN-PoliMi-UniPv

- Regulatory Aspects
  A.Serra (CNAO)
- Clinical trial procedure for BNCT
  E. Orlandi (CNAO)+ P. Pedrazzoli (UniPv)
- Radiobiology
  A. Facoetti (CNAO) + C. Ferrari (UniPv) +
  F. Ballarini (UniPv)
- Computational dosimetry and Treatment Planning
  G. Magro (CNAO) + I. Postuma (INFN-Pv) +
  P. Cirrone (INFN-LNS)
- Experimental and Environmental Dosimetry
  V. Conte (INFN-LNL) + S. Agosteo (PoliMi) +
  M. Ferrarini (CNAO)
- Boron measurement and Clinical dosimetry
  A. Retico (INFN-Pi) + N. Protti (UniPv) +
  S. Molinelli (CNAO)
- Development of new borate compounds
  G. Vago (CNAO) + G. Zanoni (UniPv)

Collaboration Agreement
CNAO-INFN-PoliMi-UniPv
signed on June 1st, 2022

CNAO
Centro Nazionale di Adroterapia Oncologica

INFN
Istituto Nazionale di Fisica Nucleare

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MILANO 1863

UNIVERSITÀ
DI PAVIA

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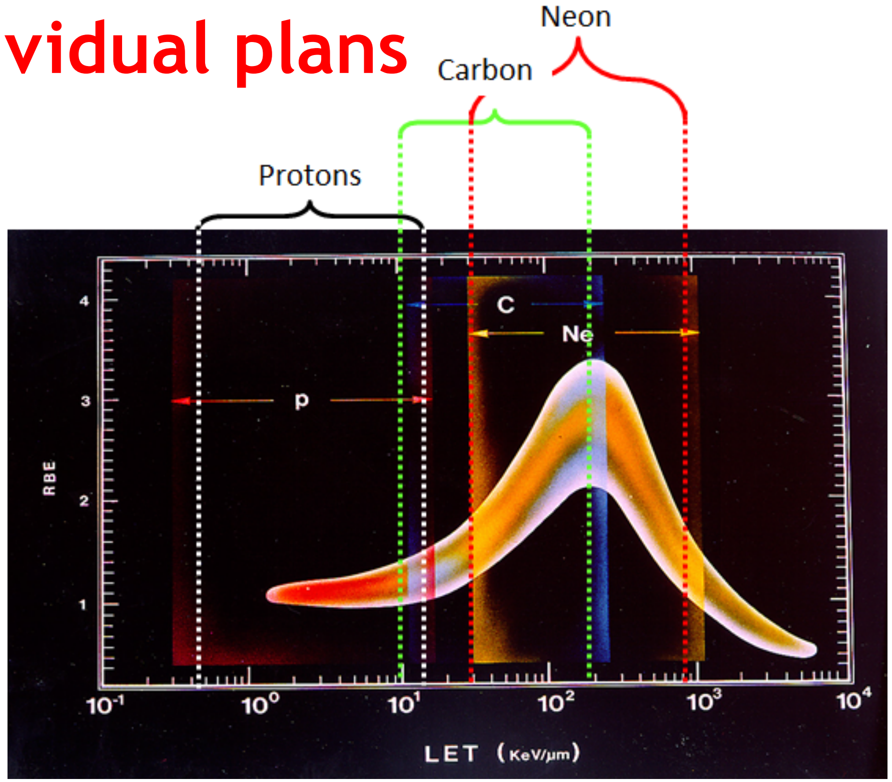
Multi-ion treatment for best individual plans

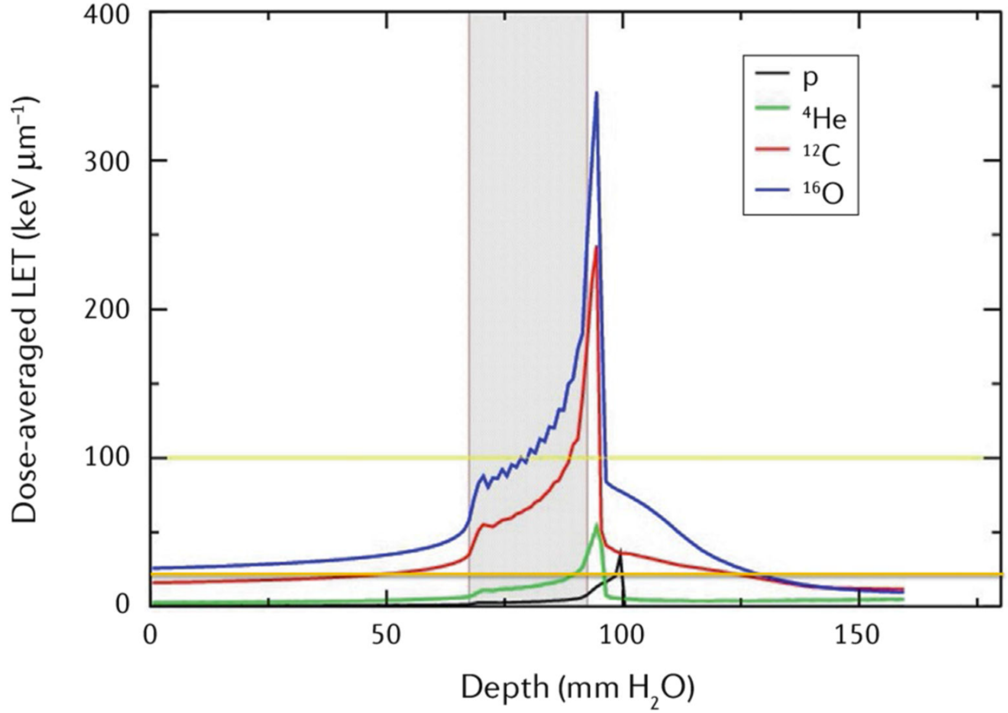
LET = *energy loss per unit mass lenght: proportional to the square of the ion charge, inversely proportional to the square of particle velocity*

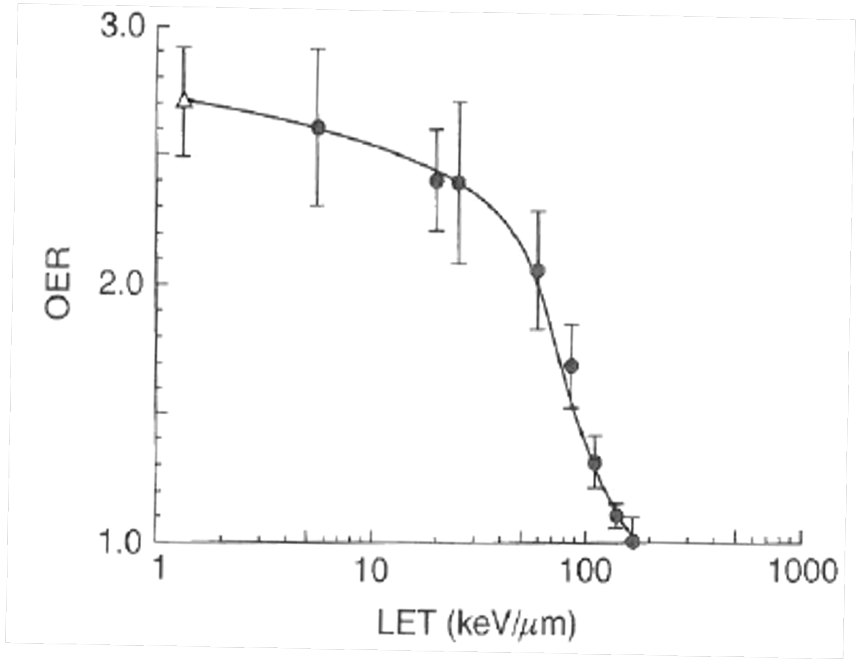
***Scattering** (good>A) - **Fragmentation** (bad>A)*

RBE = *ratio between reference dose (X rays) and particle dose to obtain the same effect*

OER = *ratio of the doses producing the same effect in hypoxic (0% pO_2) and oxic (20% pO_2) conditions*

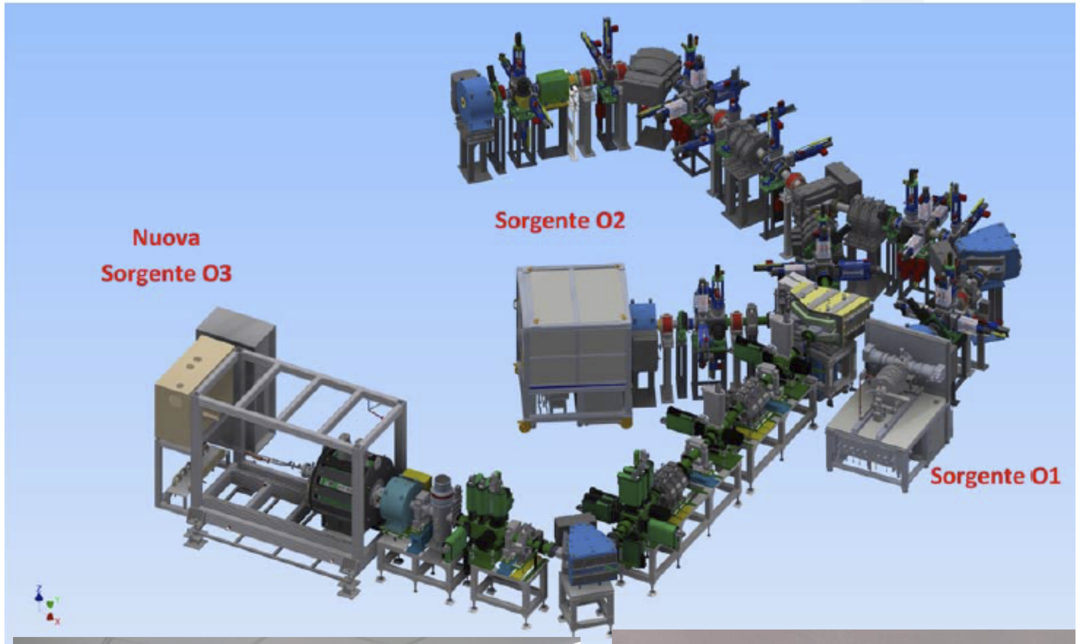


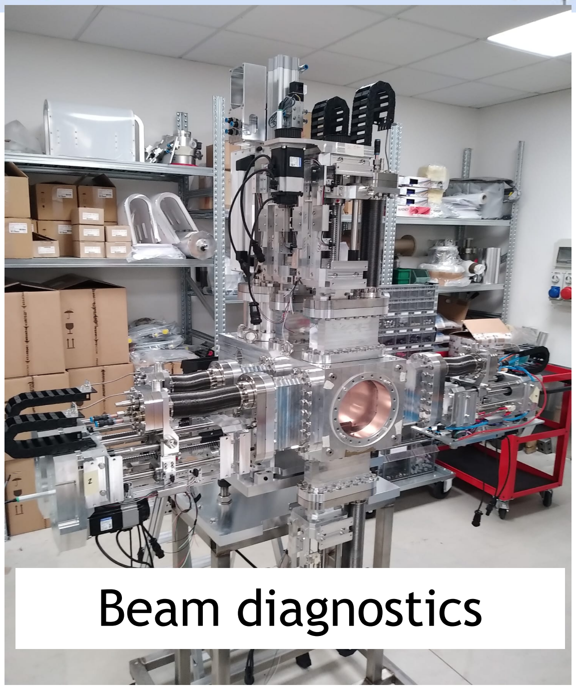




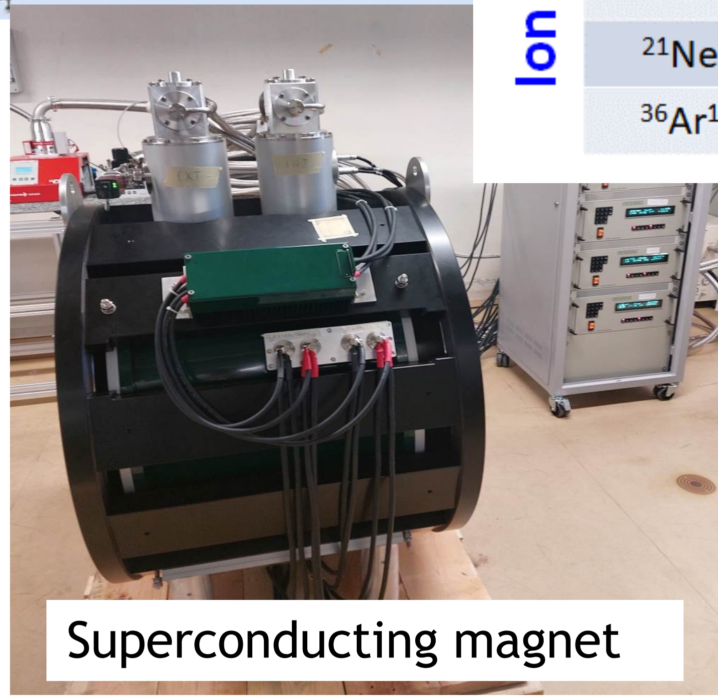
INSpIRIT: new ion source

Collaboration CNAO-INFN-HiFuture





Beam diagnostics



Superconducting magnet

Expected currents

Ion beam production (eμA)

Ion	Supernanogan (14 GHz)	AISHa (18 GHz + TFH)
H^+	2000	4000
H_2^+	1200	2000
$^3He^+$	800	2000
H_3^+	1000	1500
$^{12}C^{4+}$	250	800
$^6Li^{2+}$ - $^7Li^{2+}$	//	800
$^{10}B^{3+}$ - $^{11}B^{3+}$	//	600
$^{18}O^{6+}$	400	1000
$^{21}Ne^{7+}$	120	500
$^{36}Ar^{12+}$	20	150

Status: ongoing installation and commissioning

Ready end 2022

Ions + immunotherapy

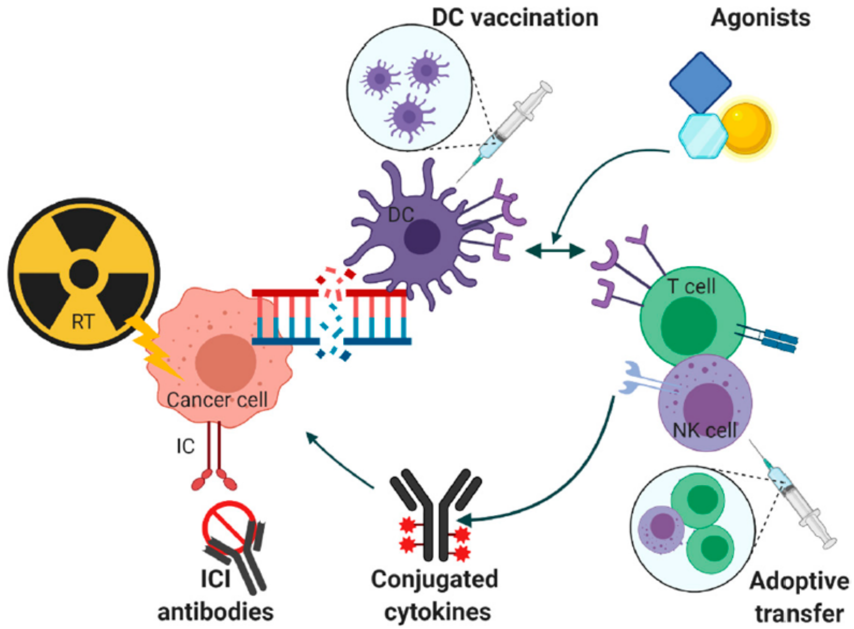


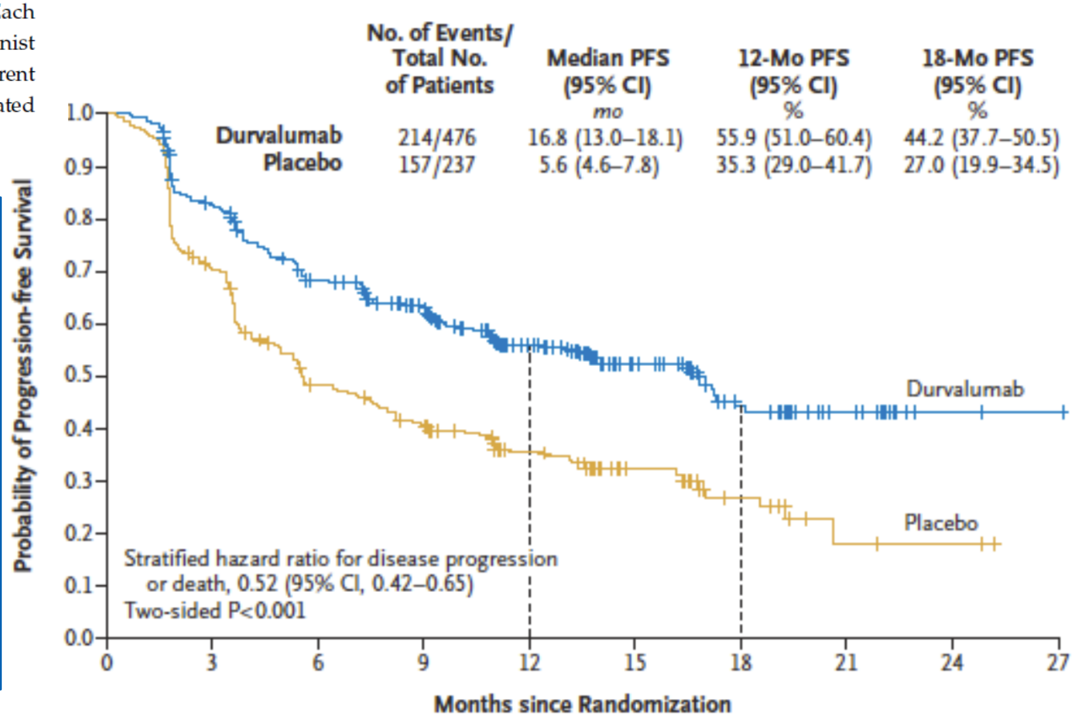
Figure 1. Combination of radiotherapy (RT) and different immunotherapeutic modalities. Each modality, such as dendritic cell vaccination, adoptive transfer of natural killer and T cells, agonist administration, conjugated antibodies or immune checkpoint inhibitors (ICIs), intervenes at different components of the immunological response chain. RT is able to synergize with all modalities. Created with BioRender.com.

Immunotherapy has become the standard of care in different advanced malignancies. However, the response rate varies according to the cancer under study and to the line of treatment.

A significant milestone in oncology was the improvement of both progression-free and overall survivals **adding immunotherapy** (anti-PD-L1 agent) **to chemo-radiation in** locally advanced unresectable non-small cell lung cancer (**NSCLC**) patients *(Antonia SJ & Özgüroğlu M, N. Engl. J. Med. 2018)*.

Charged particle radiation is thought to have greater immunogenic potential compared to photon radiotherapy due to more lethal unrepaired damage, higher ionization density and thus more complex clustered DNA lesions.

(D. Marcus et al, Cancers 2021, 13, 1468)



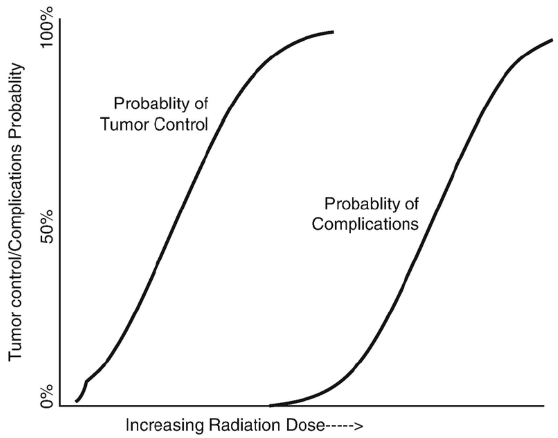
FLASH RT: what's that …

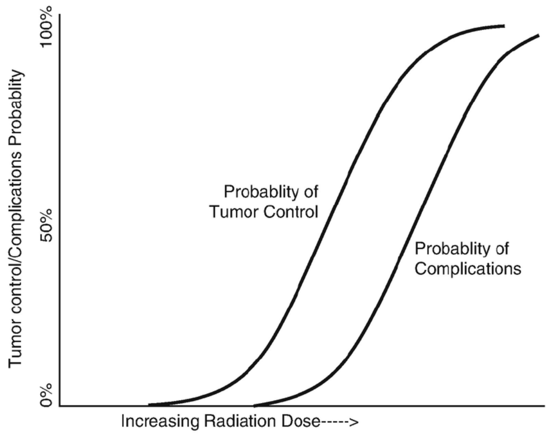
- FLASH Radiotherapy, is a novel approach of radiotherapy using ultra-high dose rate

(>40 Gy/s overall dose rate, for a total irradiation time <100 ms , but much higher rates (up to 10^9 Gy/s) during each pulse)

aiming to get **unchanged tumor control** and **protection in the normal tissue.**

FLASH RT



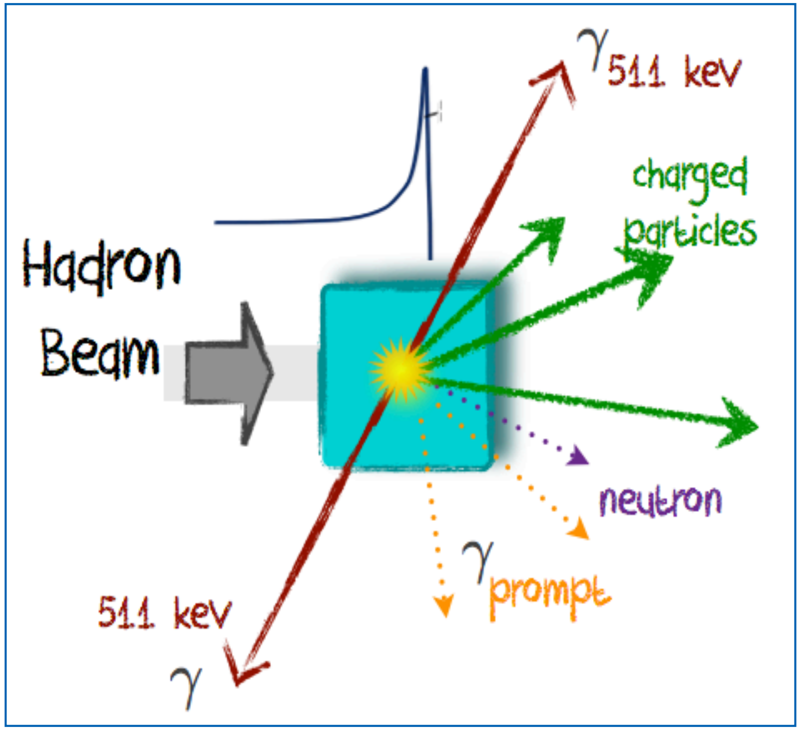


Conventional RT

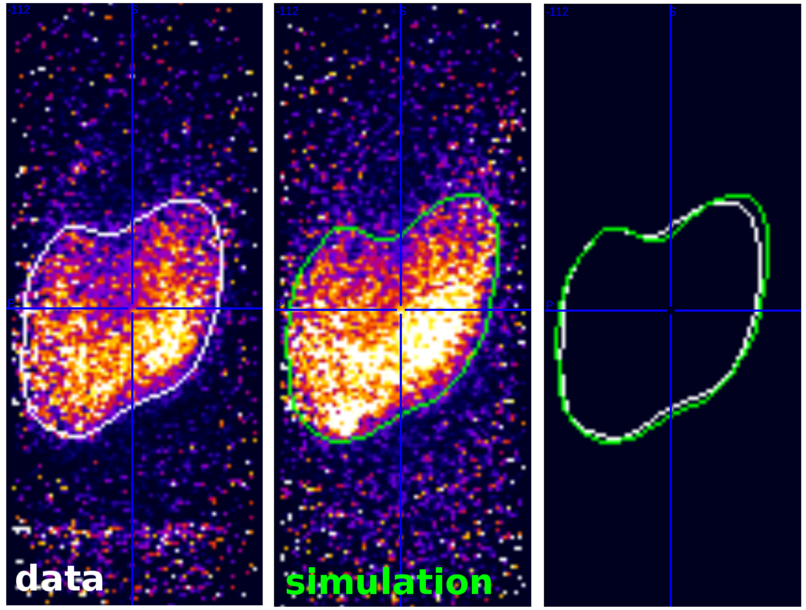
(Borrowed from Marco Durante – INSPIRE Webinar 2022)

Minibeam - grid configuration to save healthy cells in the entry channel

Dose and Beam range monitoring

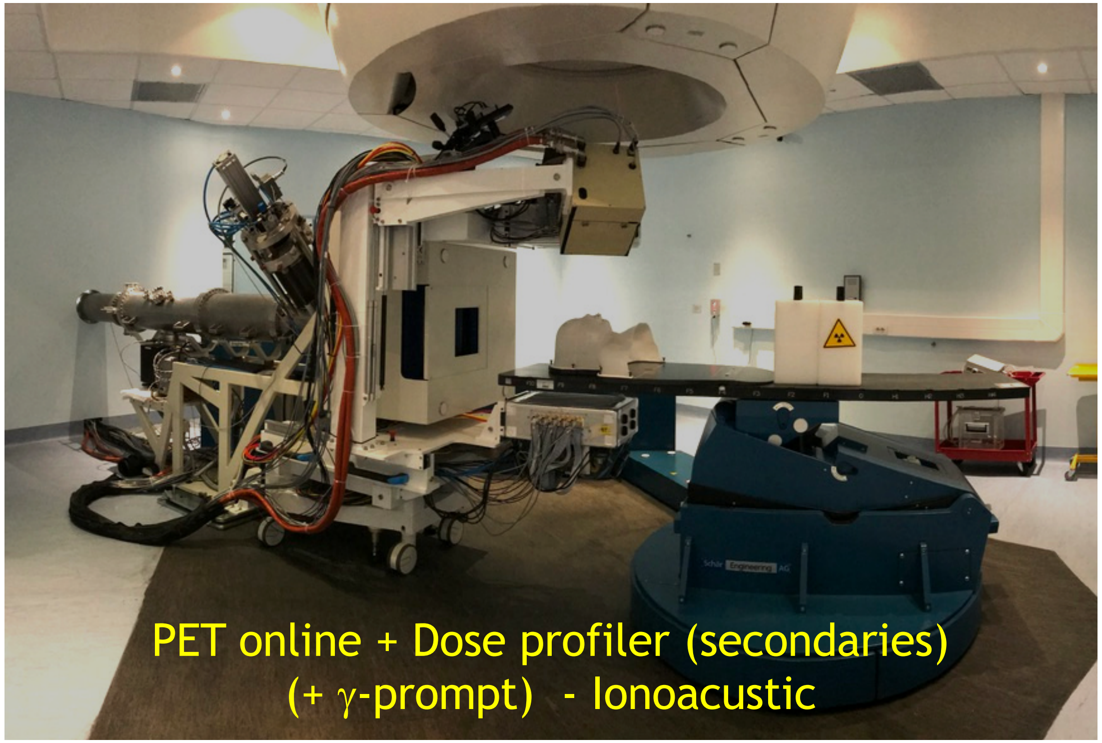


Patient - 01/12/2016
Proton beam
4 min treatment + 1min after



Goal: dose monitoring
pre-treatment
range assessment

(Collaboration with INFN
UniPi - UniTo)

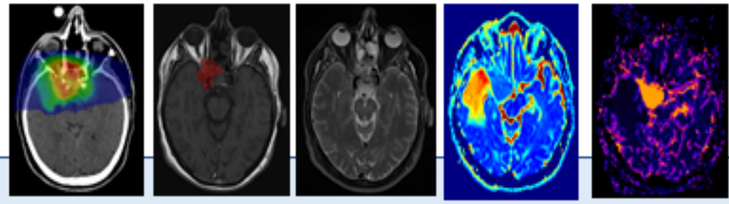


Radiomics, Dosiomic …

strategies for individual treatment optimization
and outcome prediction (Collaboraboration with PoliMi)

AIRC IG-2020 n. 24946
PI: Prof. Baroni G.

MULTI-PARAMETRIC IMAGING



CT + dose maps
Anatomical MRI (T1-w, T2-w)
Quantitative MRI (DWI, PWI,…)

Technical framework

PRE-PROCESSING
image segmentation, intensity normalization, …

FEATURE EXTRACTION
Radiomics, Dosiomics, candidate features, biomarkers, …

MACRO
modelling of properties at the MACRO level (e.g. DWI, PWI,…)

MICRO
modelling of properties at the MICRO level (e.g. cellularity)

MACHINE LEARNING-BASED MODELS

KNOWLEDGE-BASED RADIOBIOLOGICAL / STRUCTURAL MODELS
Tumour control probability (TCP), NTCP, microstructural model, …

VALIDATION

TECHNICAL

BIOLOGICAL – CLINICAL

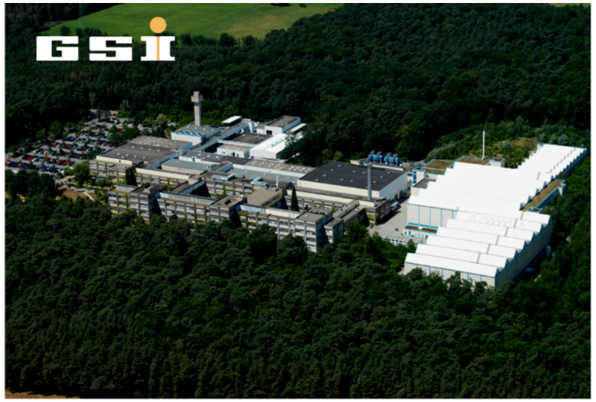
Objectives and Outline

Objectives:

- ✓ present the status of hadrontherapy against cancer
- ✓ most interesting challenges to sustain development of hadrontherapy

Outline:

- ✓ Technologies applied to hadrontherapy
- ✓ Clinical results and future developments
- ✓ Optimization of patient treatments
- ✓ Concluding remarks



HITRIplus PARTNERS

Project start: April 2021- Duration: 4 years

- CNAO
- BEVATECH
- cea
- CERN European Organisation for Nuclear Research
- Laboratorio Nacional de Fusión Ciemat
- COSYLAB
- GSI Helmholtzzentrum für Schwerionenforschung
- INFN Istituto Nazionale di Fisica Nucleare
- MedAustron
- PAUL SCHERRER INSTITUT PSI
- RIGA TECHNICAL UNIVERSITY
- SEEIIST South East European International Institute for Sustainable Technologies
- UKGM UNIVERSITÄTSKLINIKUM GIESSEN UND MARBURG
- UNIVERSITÄTSKLINIKUM HEIDELBERG
- L-Università ta' Malta
- Philipps Universität Marburg
- UPPSALA UNIVERSITET / UPPSALA UNIVERSITY SWEDEN
- wigner
- KLINIČKI CENTAR Crne Gore
- Jožef Stefan Institute
- SENTRONIS a SENIS company
- Cyril and Methodius University in Skopje

22 Institutes from 14 EU Countries
(4 CIRT centres, 10 res. inst., 5 universities, 3 SMEs)

www.hitriplus.eu

HITRI plus
Heavy Ion Therapy Research Integration

CNAO Personnel

Total number: 138

Women: 73
Mean age: 40

Men: 65
Mean age: 40

Graduates: 79% (39% PhD)

Positions: 20

Disciplines: 12

Collaboration agreements

NATIONAL

INFN

University of Milan

University of Pavia

Polytechnic of Milan

TERA Foundation

INTERNATIONAL

CERN (Geneva)

GSI (Darmstadt)

IN2P3 (F)

NIRS (Chiba)

Thank you

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

H. Ford

CNAO
Centro Nazionale di Adroterapia Oncologica