Misura di dose durante il trattamento adroterapico

Radiotherapy & Hadrontherapy
The physics of Hadrontherapy
Monitoring the Dose
Summary & conclusions

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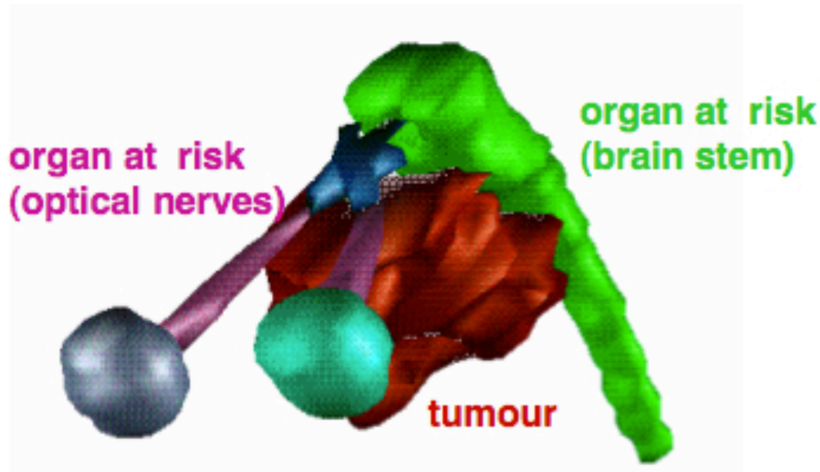
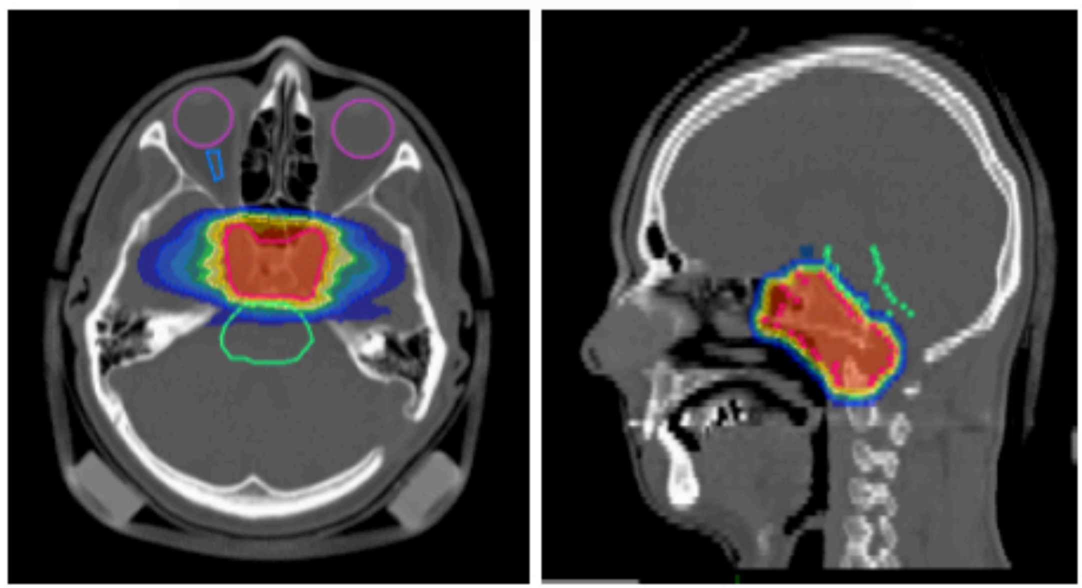
Introduction to hadrontherapy

- **Goal**
  - Deliver a high radiation dose to the target area to kill all tumour cells.
  - Spare out healthy tissue and organs at risk.
  - Tumour conformal dose distribution.
- **Radiation type**
  - Conventional therapy: electrons, photons
  - Hadron therapy: protons, light ions
  - More exotic: neutrons, pions





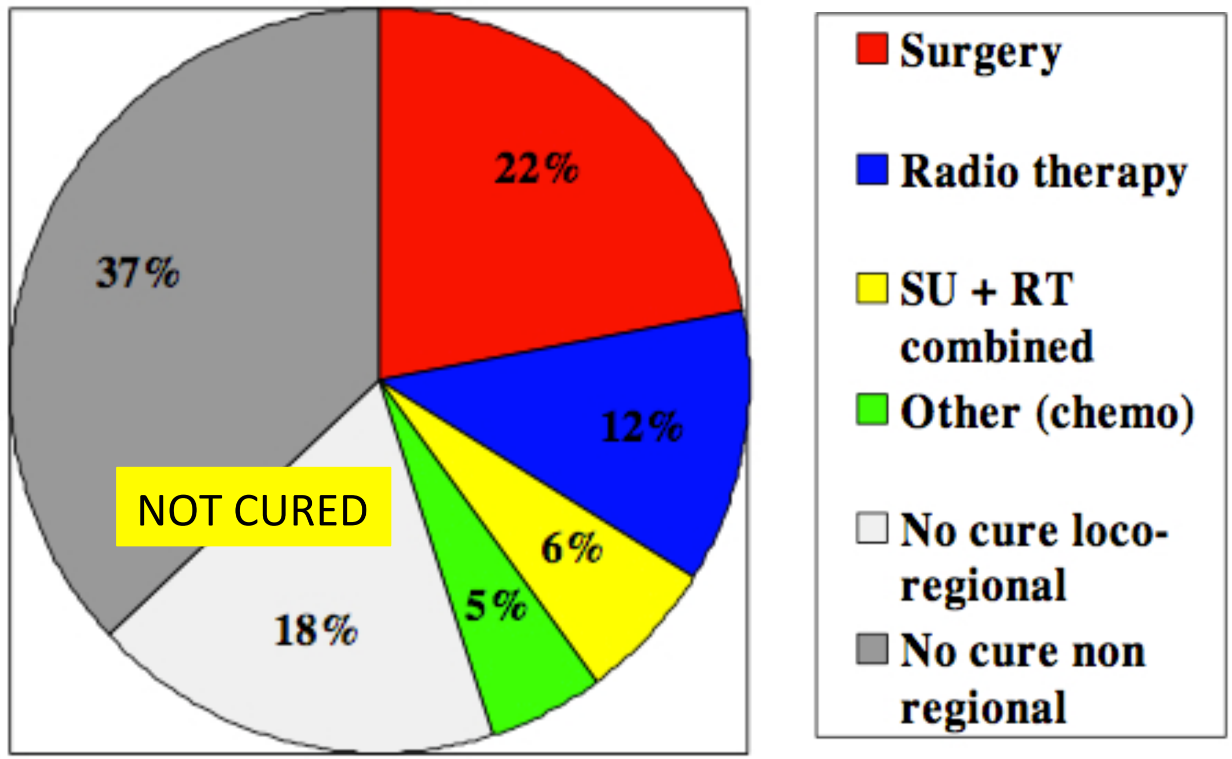
Courtesy GSI

Tumor treatment in Europe

Percentage of cure ~ 45% (EU report 2000)

Main problems:

- Anatomy does not permit surgery
- RadioResistant tumours or close to organs at risk (OAR)



Hadrontherapy can be a viable solution to increase cure to 60-65%: allows for better localised dose distribution

POTENTIAL PATIENTS

X-ray therapy (5 – 20 MeV)

20'000 pts/year every 10^6 inhabitants

Protontherapy

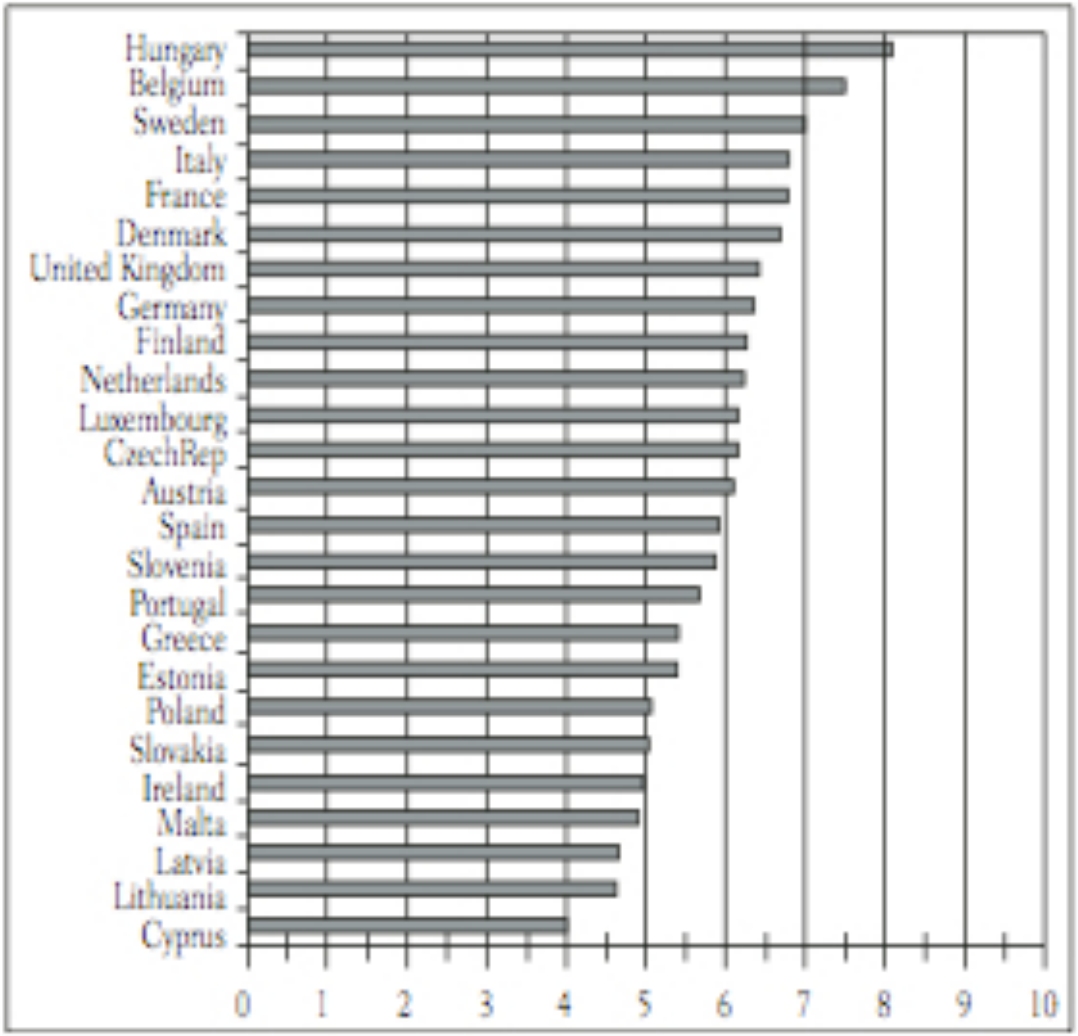
10% of X-ray patients

2'000 pts/year every 10 M

Carbon ions for radioresistant tumours
10% of X-ray patients

2'000 pts/year every 10 M

By TERA foundation



EU Report : LINAC needed per 10^6 inhabitants

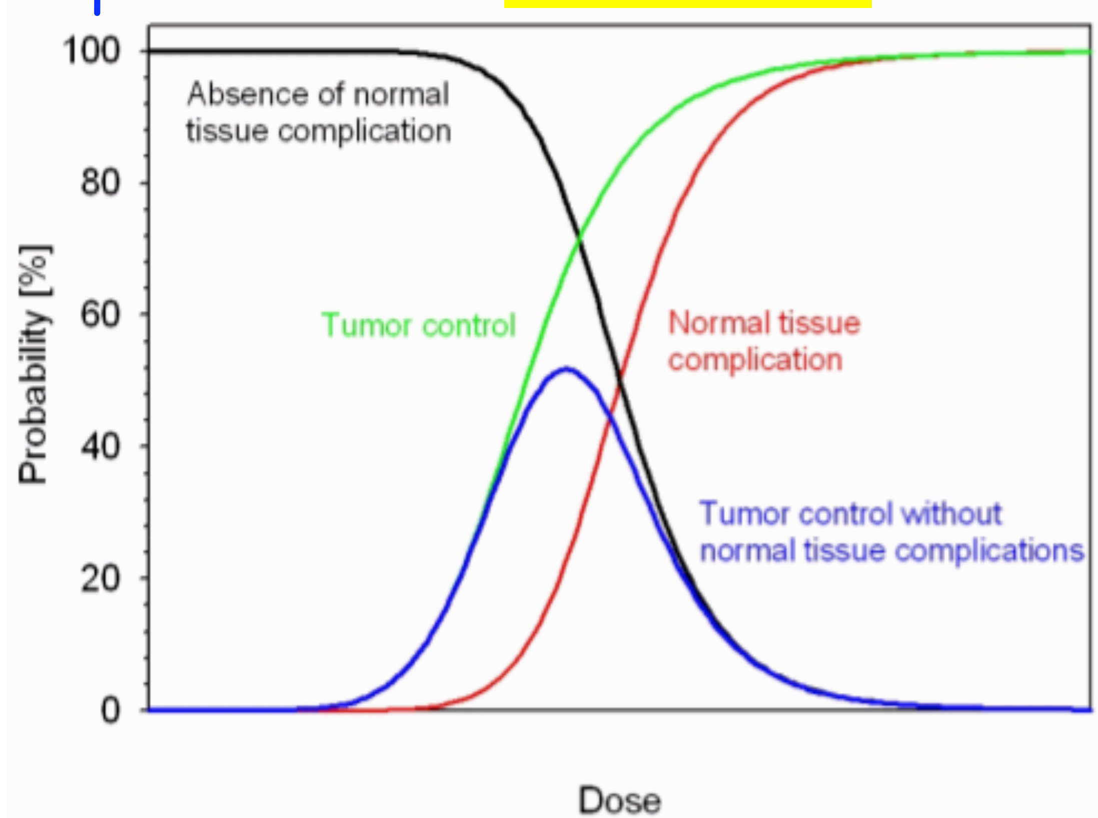
Radiotherapy

- Part of multi-disciplinary approach to cancer care
- Useful for 50-60% of all cancer patients (also together surgery)
- Can be given for cure or palliation

- Mainly used for loco-regional treatment
- Benefits and side-effects are usually limited to the area(s) being treated

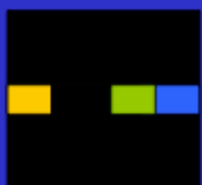
$$Dose = \frac{dE_{abs}}{dm} (Gray)$$

Therapy window



DNA is the most important molecule that can be changed by radiation

- **Effects of DNA Damage**

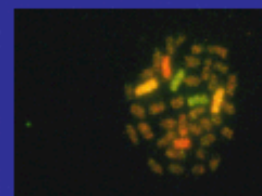


Gene Expression

A gene may respond to the radiation by changing its signal to produce protein. This may be protective or damaging.

Gene Mutation

Sometimes a specific gene is changed so that it is unable to make its corresponding protein properly



Chromosome Aberrations

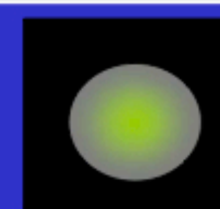
Sometimes the damage effects the entire chromosome, causing it to break or recombine in an abnormal way. Sometimes parts of two different chromosomes may be combined

Side Effects

Genomic Instability

Sometimes DNA damage produces later changes which may contribute to cancer.

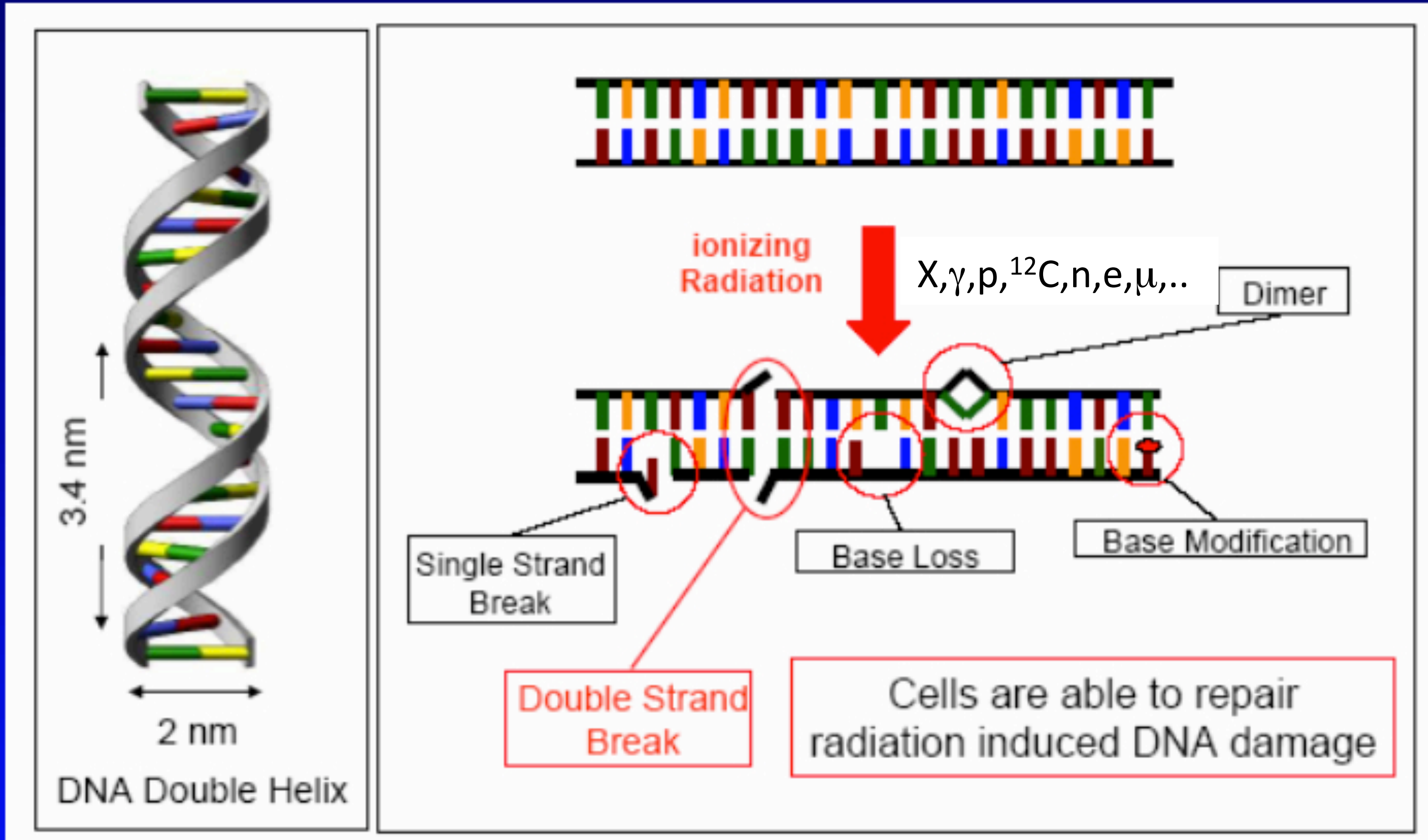
RadioTherapy



Cell Killing

Damaged DNA may trigger apoptosis, or programmed cell death. If only a few cells are affected, this prevents reproduction of damaged DNA and protects the tissue.

Studies have shown that most radiation-induced DNA damage is normally repaired by the body

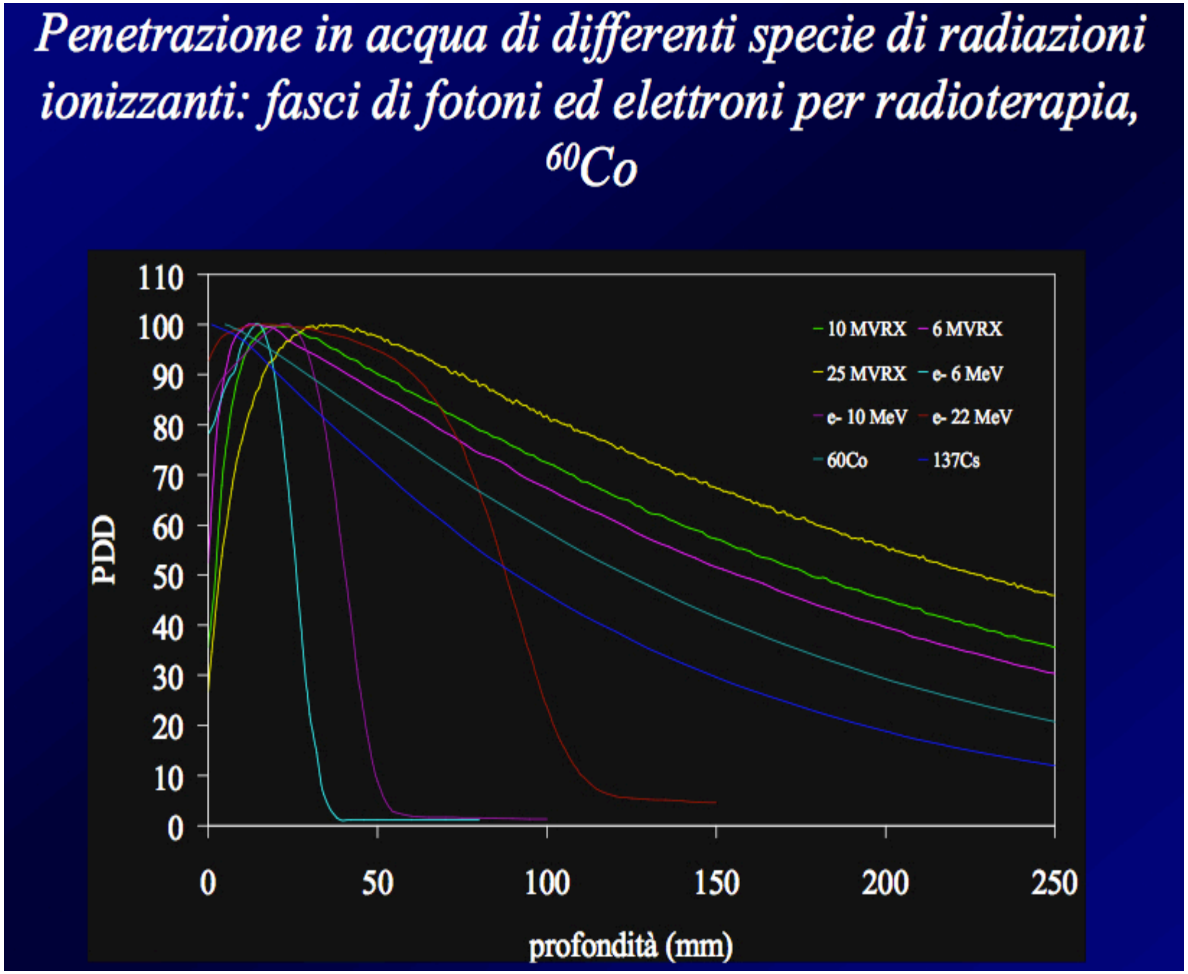


Packed in the 5-10 μm radius of the cell nucleus

SSB	1000
DSB	30-40
DNA-Protein Crosslinks	50
Complex Damage (SSB+Base lesion)	60

The photon based RT

The photon (and e^-) beams are the most common in RT. They are not so expensive, small, and reliable.



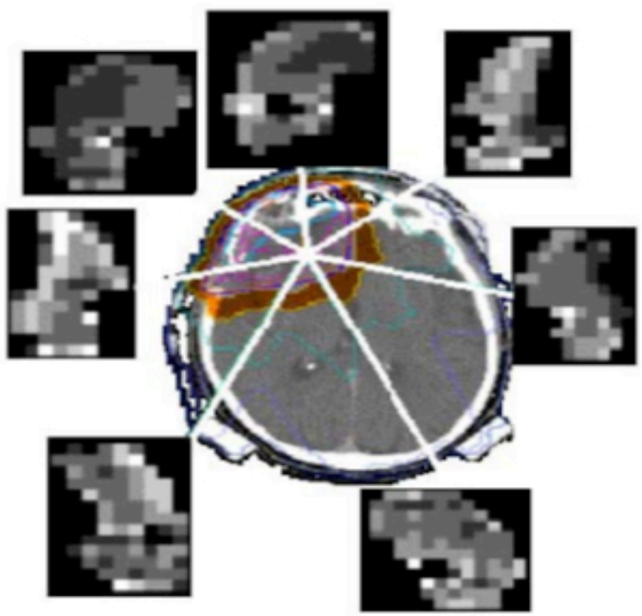
It's a pity that the energy release shape is not so suitable to release dose in a deep tumor

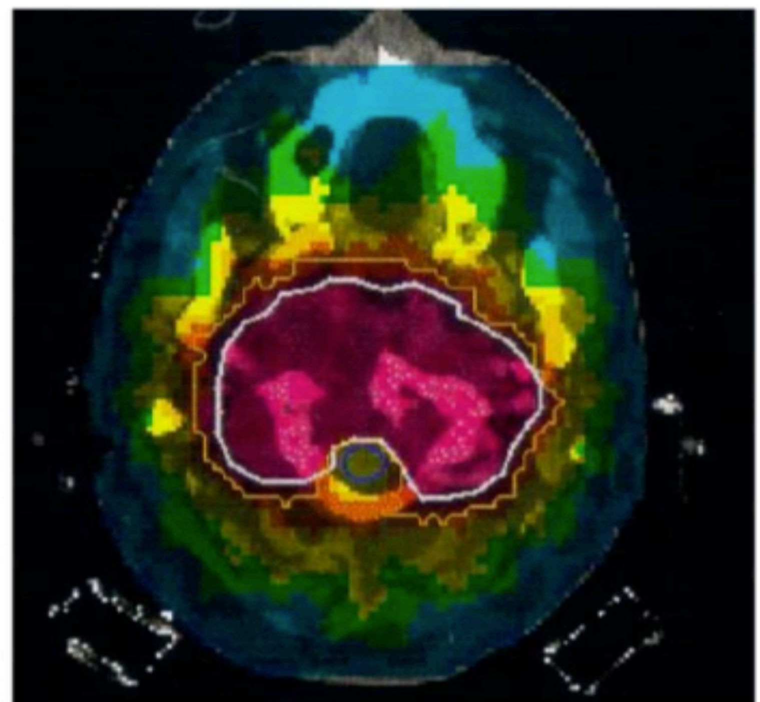
(remember the exponentian attenuation law..?).

But….

State of the art photon Radiotherapy: IMRT

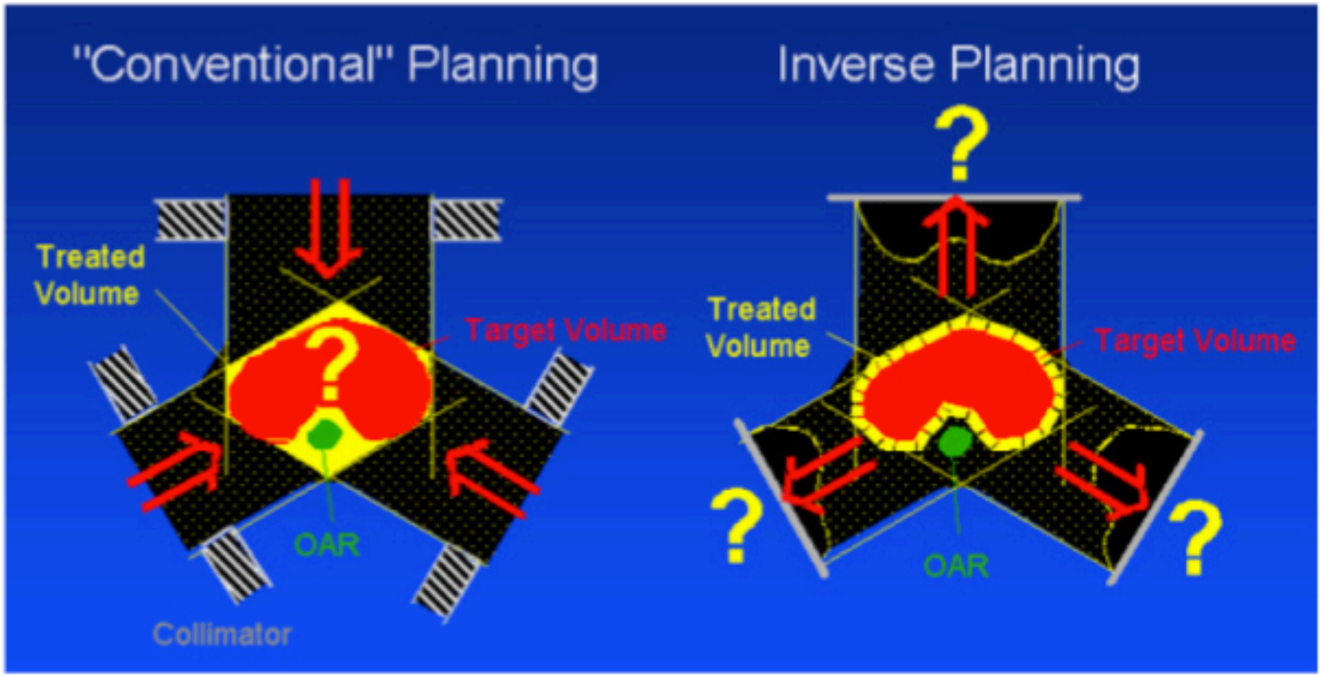
The use of sophisticated imaging (CT), the superposition of several beams, computed optimization and multi-leaves collimators makes the miracle!!





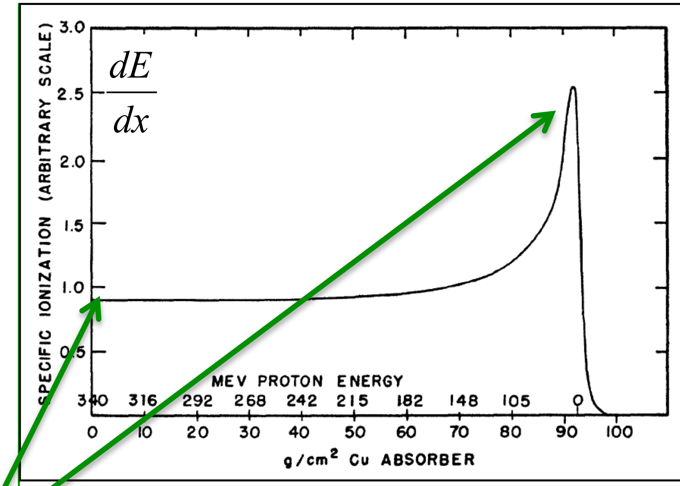
Treatment Planning System (TPS)

- Based on the CT data-> geometrical model of the treatment region included density info
- Meet target dose prescription and avoid OAR
- Optimization of machine and collimators parameters to achieved the target dose distribution
- Huge use of MC calculation

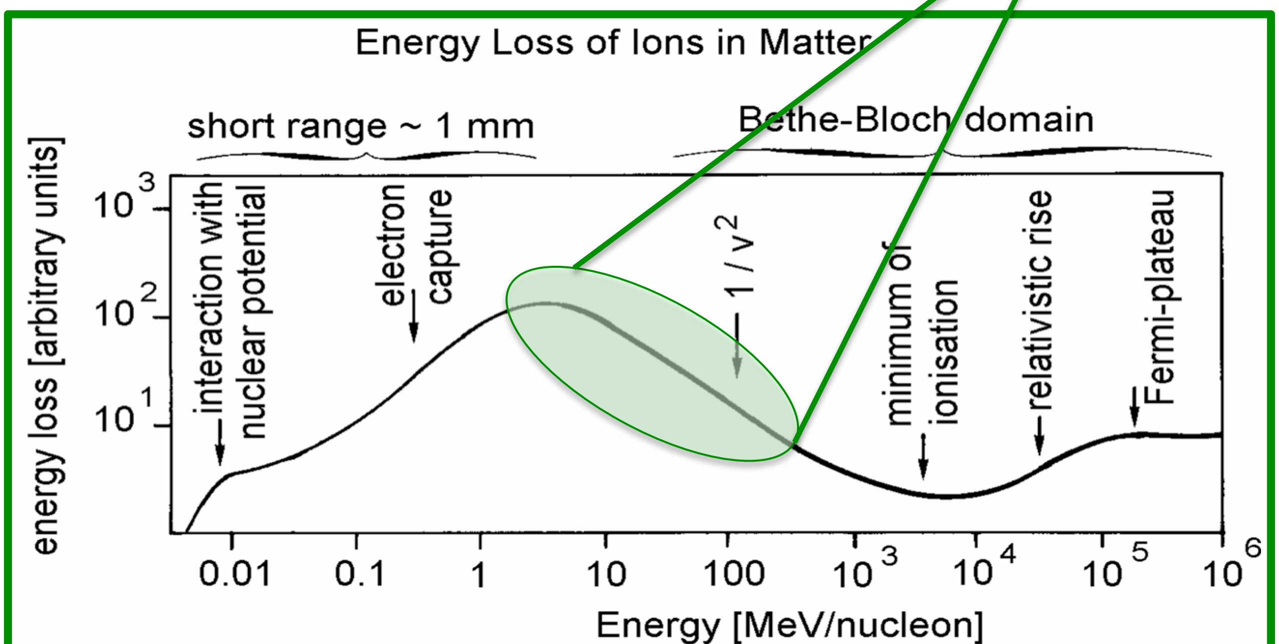


But physics can help…

On the other hand, the release of energy by charge particles has very different, and attractive, features… why not to use them? (Wilson 1946)



lunghezza di penetrazione

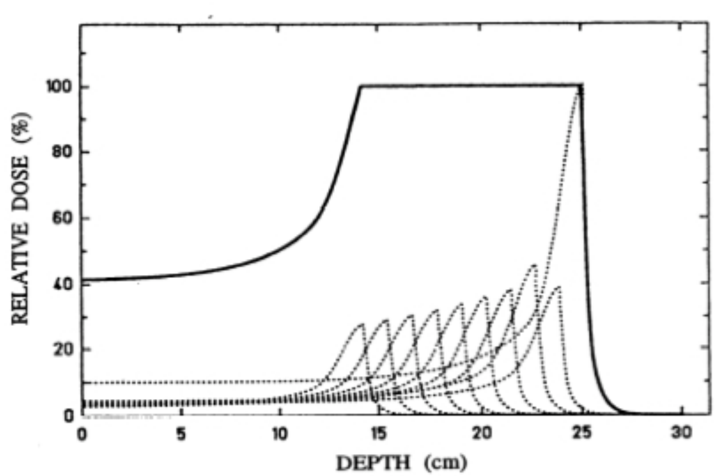


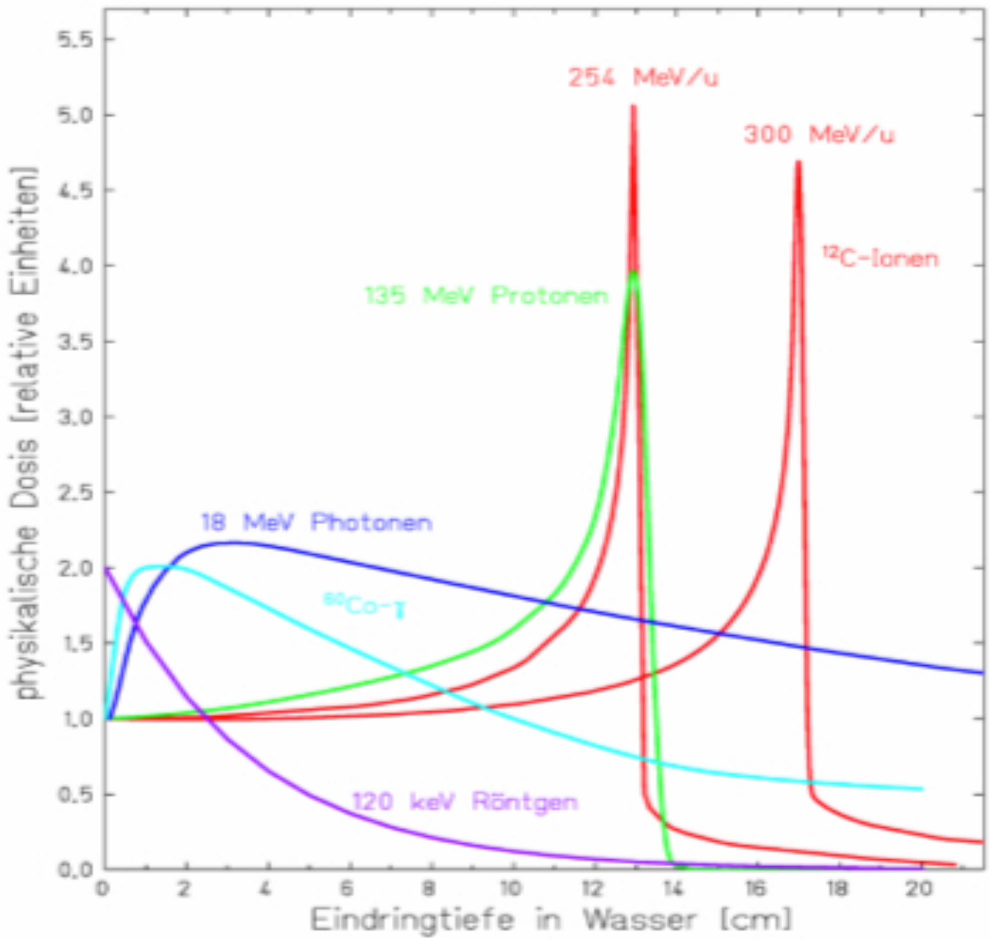
Perfect to release energy (dose) in a tumor buried inside the patient, like a depht bomb..

Hadrontherapy vs Photon RT

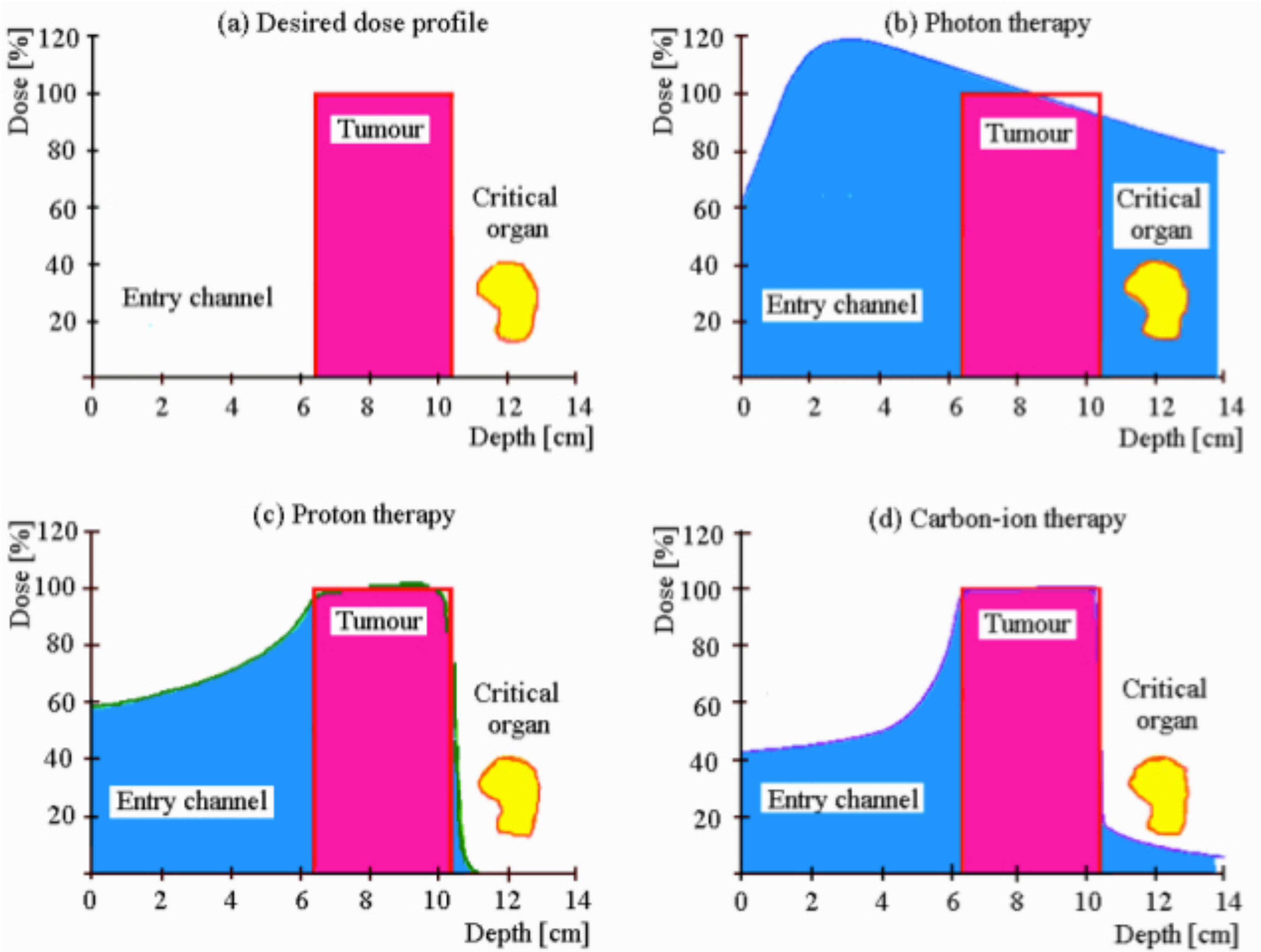
The highest dose released at the end of the track, sparing the normal tissue

- Length of track function of the beam energy
- Dose decrease rapidly after the BP.
- Accurate conformal dose to tumour with Spread Out Bragg Peak



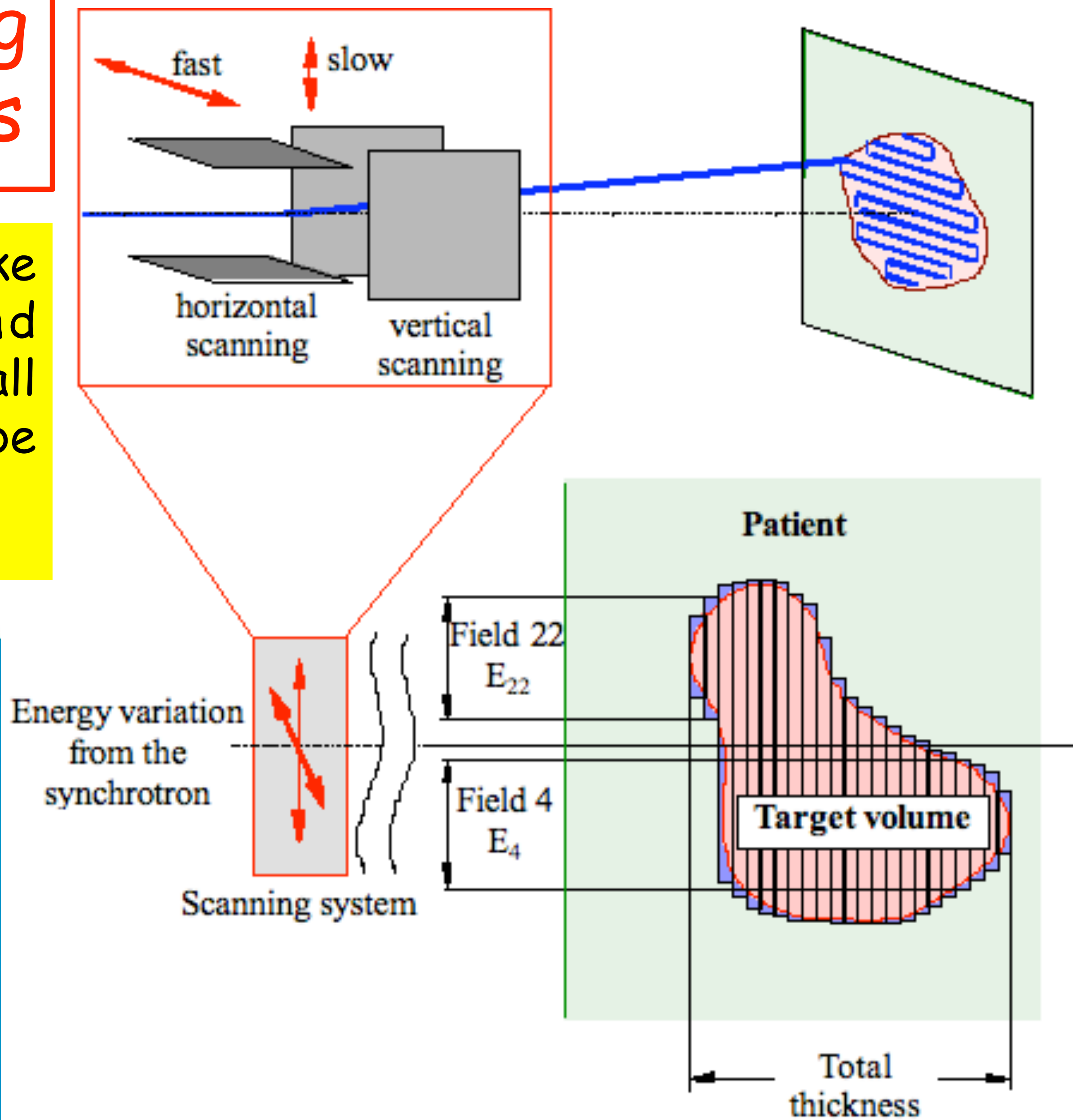


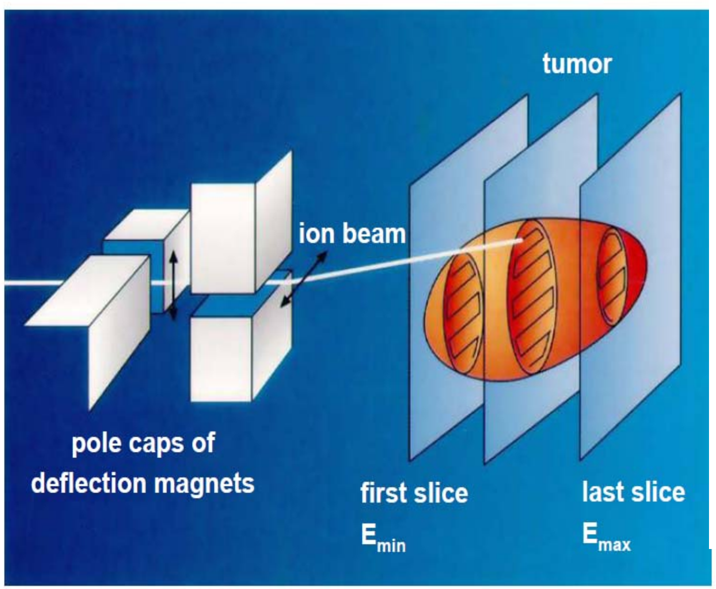
Single Field Dose comparison



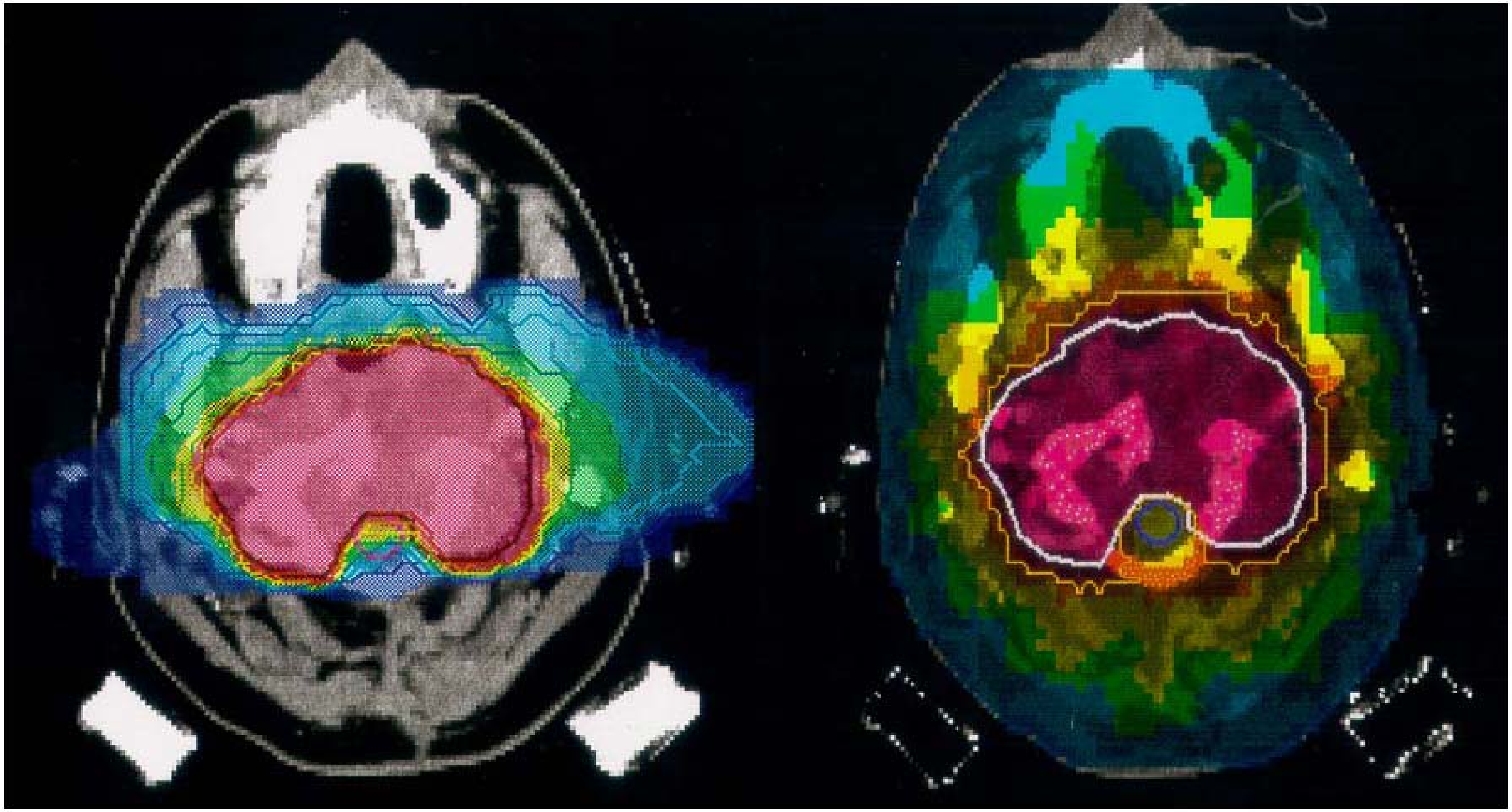
Active Scanning by pencil beams

Moving the 12C beam like in an old TV-set and changing the energy, all the tumor region can be treated->synchrotron





Comparison ^{12}C vs IMRT



C-12, 2 fields IMRT, 9 fields

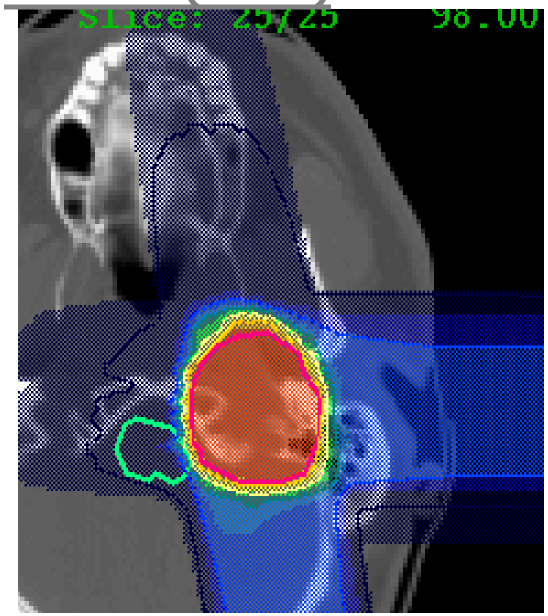
Courtesy of M.Durante, GSI

Protons vs ^{12}C

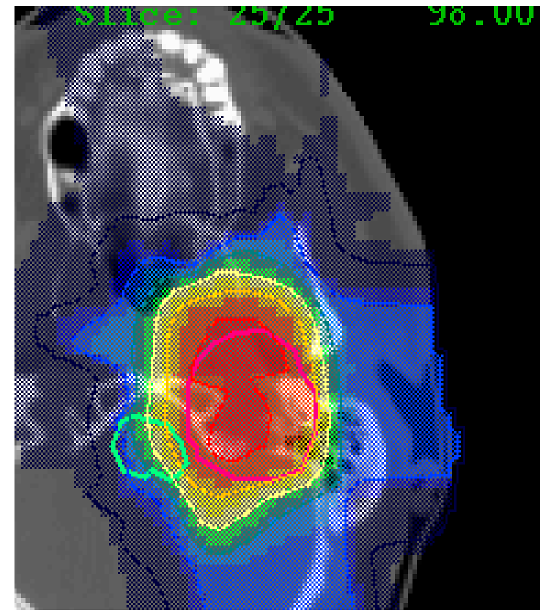
No absolute best: (if you exclude that the proton facilities are less expensive..). For example...

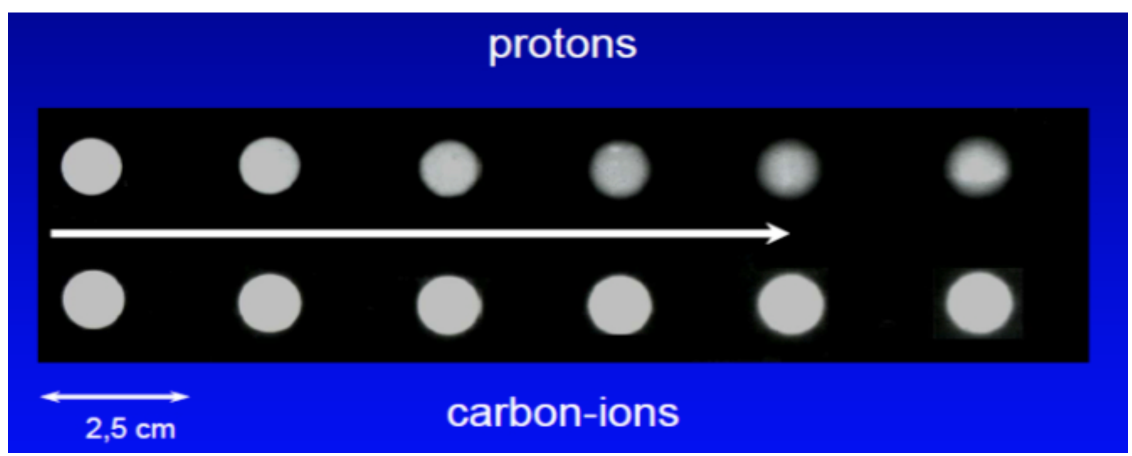
- ^{12}C has better peak to plateau dose ratio
- ^{12}C has less multiple scattering

C-ions (GSI)



H-ions (CapeTown, SA)





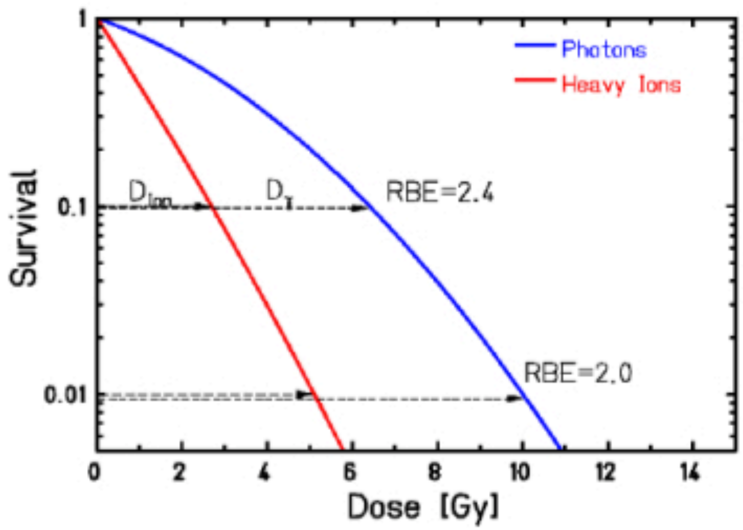
Is ^{12}C the best projectile? Cell Survival

Relative **B**iological **E**ffectiveness

Due to the high LET (Linear Energy Transfer ~ De/Dx), the carbon ions is much better at killing the tumour cells wuth respect to the X rays for a given dose released ➔high RBE

$$S = \frac{N_{col}}{N_{seed}} = e^{-(\alpha D + \beta D^2)}$$

Comparison of dose values at **Isoeffect-Level!**

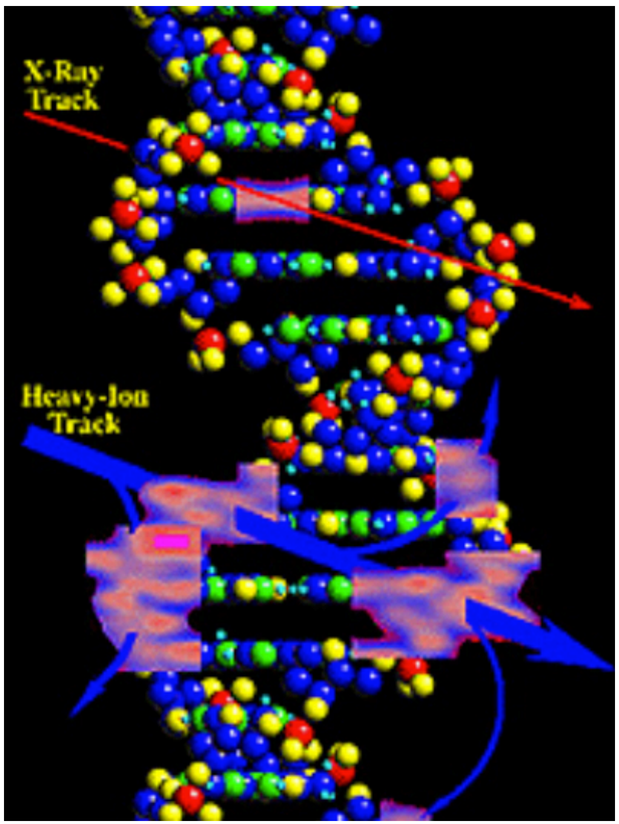


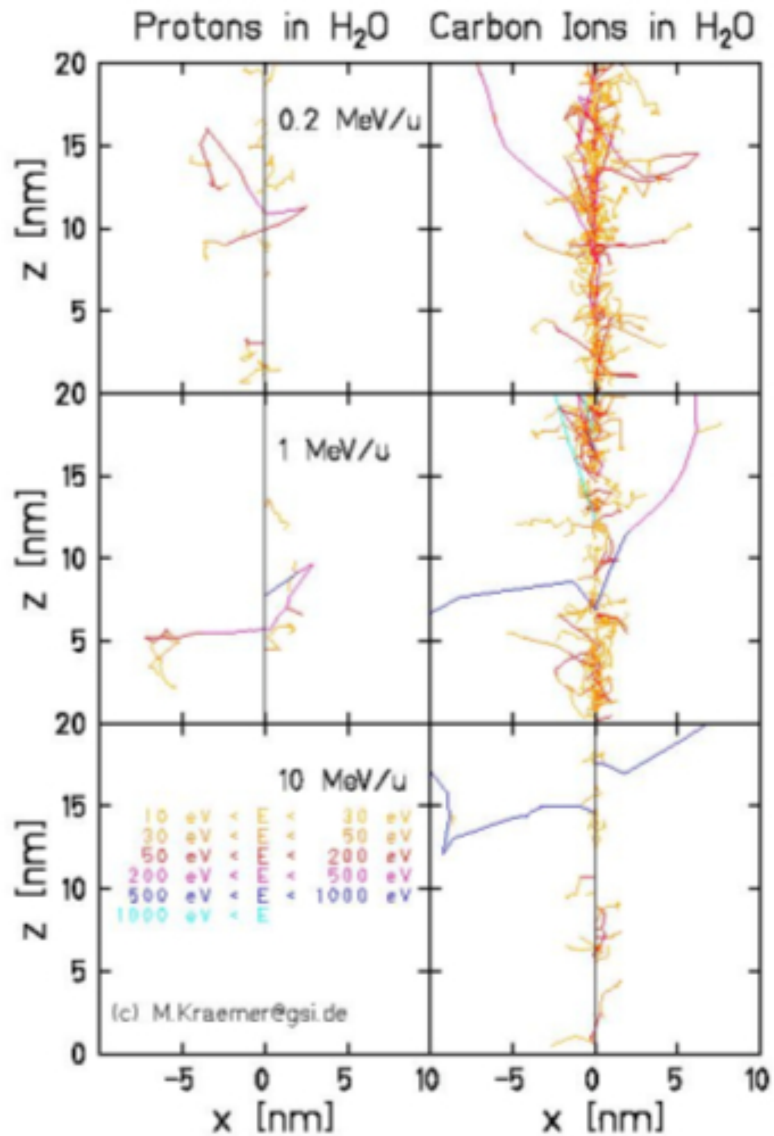
$$RBE = \left.\frac{D_{\gamma}}{D_{Ion}}\right|_{Isoeffect}$$

α[Gy^{-1}]: initial slope
β[Gy^{-2}]: bending of curve
α/β[Gy]: dose, at which contribution from linear term = contribution from quad. term

Why same dose induces different survival?

The high ionization density of ^{12}C induces easily DSB in DNA helix



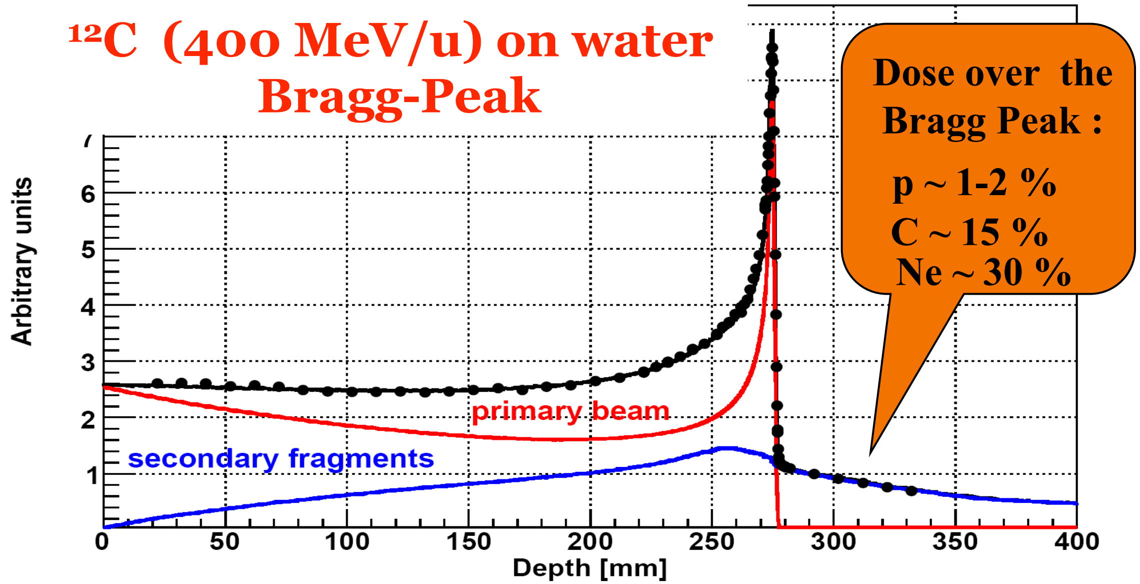


BUT …. ^{12}C fragments on the path to tumour

Dose release in healthy tissues with possible long term side effects, in particular in treatment of young patients ➔must be carefully taken into account in the Treatment Planning System

- ✓ Production of fragments with higher range vs primary ions
- ✓ Production of fragment with different direction vs primary ions

- ✓ *Mitigation and attenuation of the primary beam*
- ✓ *Different biological effectiveness of the fragments wrt ^{12}C*



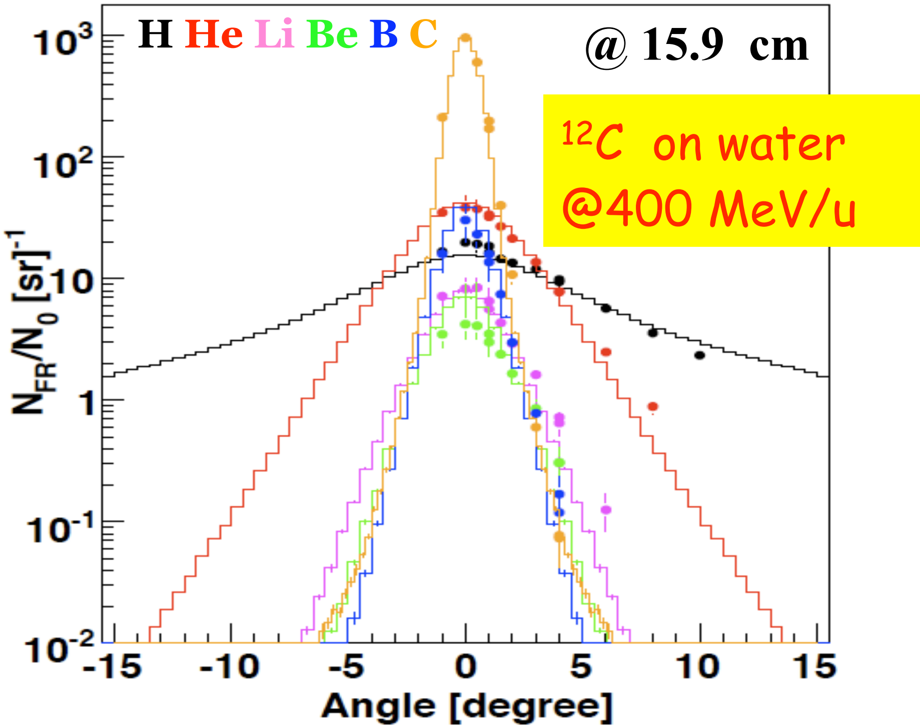
Exp. Data (points) from Haettner et al, Rad. Prot. Dos. 2006

Simulation: A. Mairani PhD Thesis, 2007, Nuovo Cimento C, 31, 2008

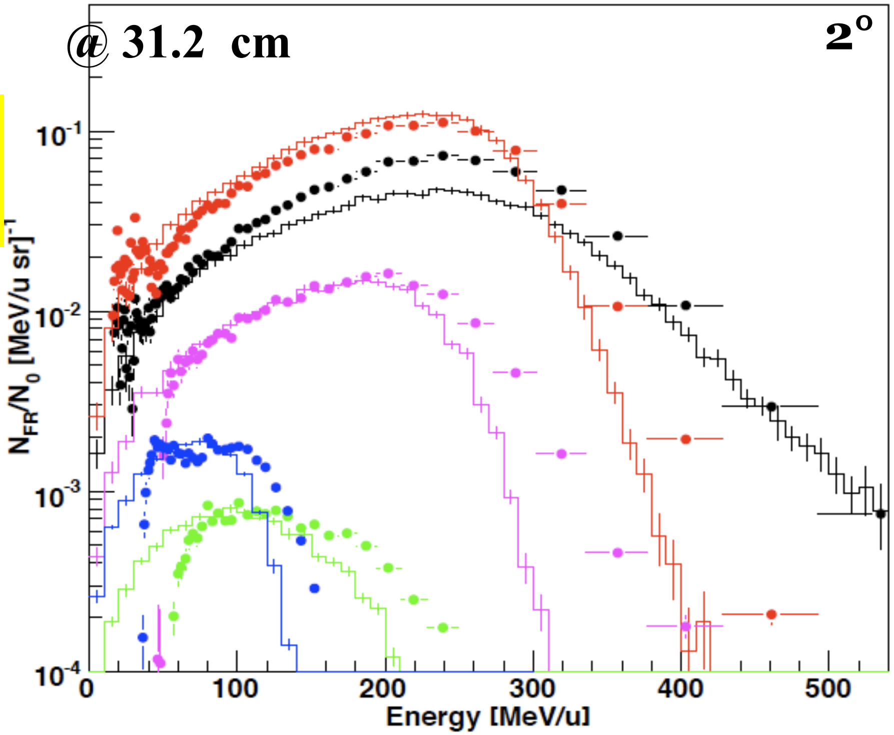
Scattered Frag.s production by ^{12}C beam

The secondary fragments broad the lateral dose profile and go beyond the tumor region.

Angular distribution



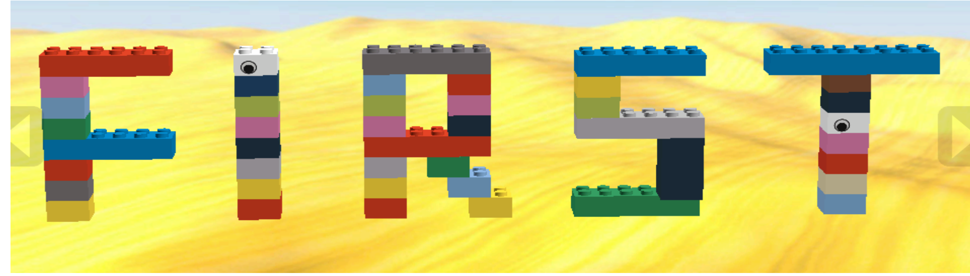
Energy distribution



FLUKA benchmark against thick target data

Exp. Data (points) from Haettner et al, Rad. Prot. Dos. 2006
Simulation: A. Mairani PhD Thesis, 2007, PMB *to be published*

The FIRST collaboration



- INFN: Cagliari,LNF,LNS,Milano,Roma3,Torino: C.Agodi, G.Battistoni, M.Carpinelli, G.A.P.Cirrone, G.Cuttone , M.De Napoli, B.Golosio, Y.Hannan, E.Iarocci, F.Iazzi, R.Introzzi, A.Mairani, V.Monaco, M.C.Morone,P.Oliva, A.Paoloni, V.Patera, L.Piersanti, N.Randazzo, F.Romano, R.Sacchi, P.Sala, A.Sarti, A.Sciubba, C.Sfienti, V.Sipala, E.Spiriti
- DSM/IRFU/SPhN CEA Saclay, IN2P3 Caen, Strasbourg, Lyon: M.D.Salsac, A.Boudard, J.E. Ducret, M. Labalme, F. Haas, C.Ray
- GSI: M.Durante, D.Schardt, R.Pleskac, T.Aumann, C.Scheidenberger, A.Kelic, M.V.Ricciardi, K.Boretzky, M.Heil, H.Simon, M.Winkler
- ESA: P.Nieminem, G.Santin
- CERN: T.Bohlen

INFN Istituto Nazionale di Fisica Nucleare

FIRST stands for: Fragmentation of Ions Relevants for Space and Therapy → S371 is the GSI label

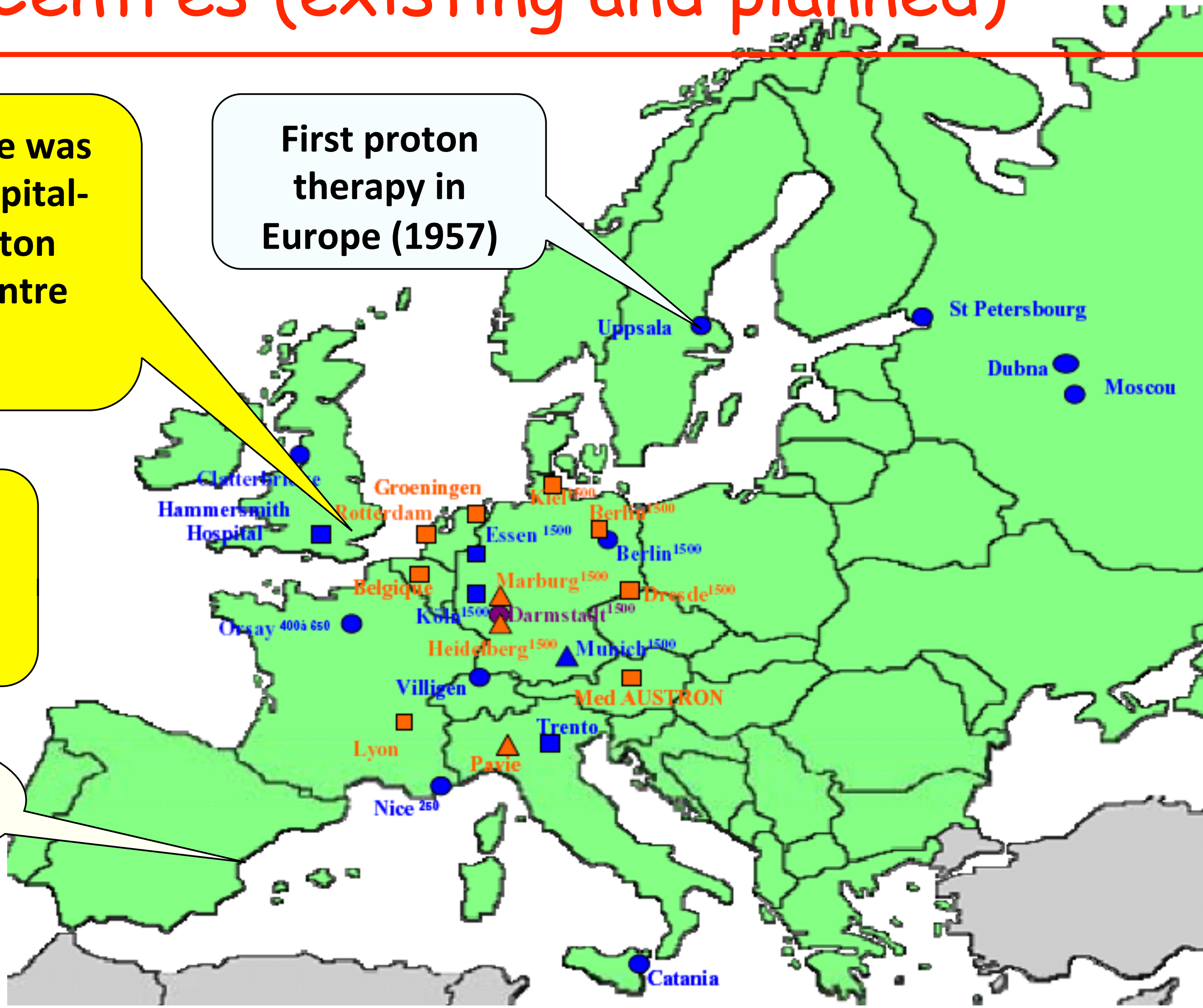
Centres (existing and planned)

Clatterbridge was the first hospital-based proton therapy centre (1989)

First proton therapy in Europe (1957)

The second UK centre MAY open in 2014!

Plans for Valencia

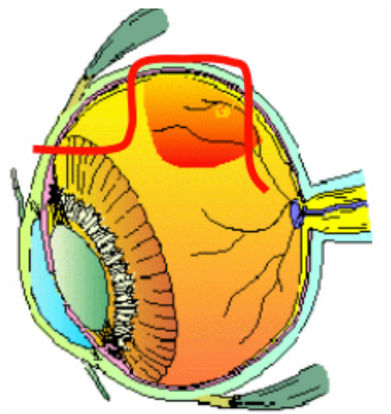


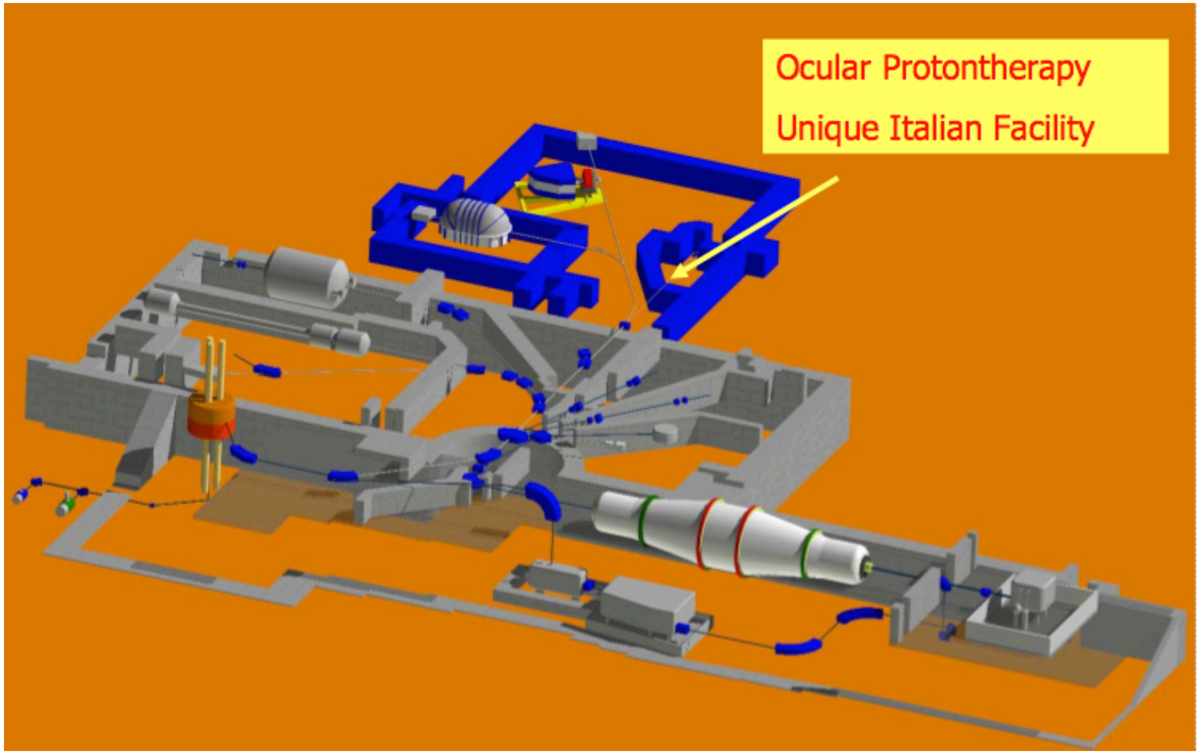
INFN & hadrontherapy CATANA @LNS

Proton 80MeV beam

Treatment of the choroidal and iris Melanoma.

In Italy about300 new cases/year





Centro di AdroTerapia ed Applicazioni Nucleari Avanzate

INFN & hadrontherapy: CNAO @Pavia

MI,TO,LNF,LNL,FE

Il Centro Nazionale di Adroterapia Oncologica

Particelle: p (60 - 250 MeV), C^{6+} (120 - 400 MeV/u)

Range del fascio: 1 → 27 g/cm²

Risoluzione del range: 0.1 g/cm²

Precisione di dose: ± 2.5 %

Dimensione fascio: 4 → 10 mm FWHM

- Accuratezza sulla dimensione: 0.2 mm
- Posizionamento fascio (passo): 1 mm
- Accuratezza posizionamento: 0.05 mm
- Dimensione del campo: 2×2 → 20×20 cm²

INFN Istituto Nazionale di Fisica Nucleare

Patient Statistics (for the facilities in operation end of 2009):

WHERE		WHAT	FIRST PATIENT	PATIENT TOTAL	DATE OF TOTAL	
Canada	Vancouver (TRIUMF)	p	1995	145	Dec-09	ocular tumors only
China	Wanjie (WPTC)	p	2004	977	Dec-09	
England	Clatterbridge	p	1989	1923	Dec-09	ocular tumors only
France	Nice (CAL)	p	1991	3935	Dec-09	ocular tumors only
France	Orsay (CPO)	p	1991	4811	Dec-09	3936 ocular tumors
Germany	Berlin (HMI)	p	1998	1437	Dec-09	
Germany	Munich (RPTC)	p	2009	78	Dec-09	
Italy	Catania (INFN-LNS)	p	2002	174	Mar-09	ocular tumors only
Japan	Chiba (HIMAC)	C ion	1994	4504	Feb-09	
Japan	Kashiwa (NCC)	p	1998	680	Dec-09	
Japan	Hyogo (HIBMC)	p	2001	2382	Nov-09	
Japan	Hyogo (HIBMC)	C ion	2002	638	Nov-09	
Japan	Tsukuba (PMRC, 2)	p	2001	1586	Dec-09	
Japan	WERC	p	2002	56	Dec-08	
Japan	Shizuoka	p	2003	852	Dec-09	
Korea	Ilsan, Korea	p	2007	519	Dec-09	
Russia	Moscow (ITEP)	p	1969	4162	Jul-09	
Russia	St. Petersburg	p	1975	1353	Dec-09	
Russia	Dubna (JINR, 2)	p	1999	595	Dec-09	
South Africa	iThemba LABS	p	1993	511	Dec-09	
Sweden	Uppsala (2)	p	1989	929	Dec-08	
Switzerland	Villigen PSI (72 MeV-Optis)	p	1984	5300	Dec-09	ocular tumors only
Switzerland	Villigen PSI (230 MeV)	p	1996	542	Dec-09	
CA., USA	UCSF - CNL	p	1994	1200	Dec-09	ocular tumors only
CA., USA	Loma Linda (LLUMC)	p	1990	14000	Oct-09	
IN., USA	Bloomington (MPRI, 2)	p	2004	890	Dec-09	
MA., USA	Boston (NPTC)	p	2001	4270	Oct-09	
TX, USA	Houston	p	2006	1700	Dec-09	
FL, USA	Jacksonville	p	2006	1847	Dec-09	
OK, USA	Oklahoma City (ProCurePTC)	p	2009	21	Dec-09	
				62017	**Total**	
			thereof	7151	C-ions	
				56854	protons	

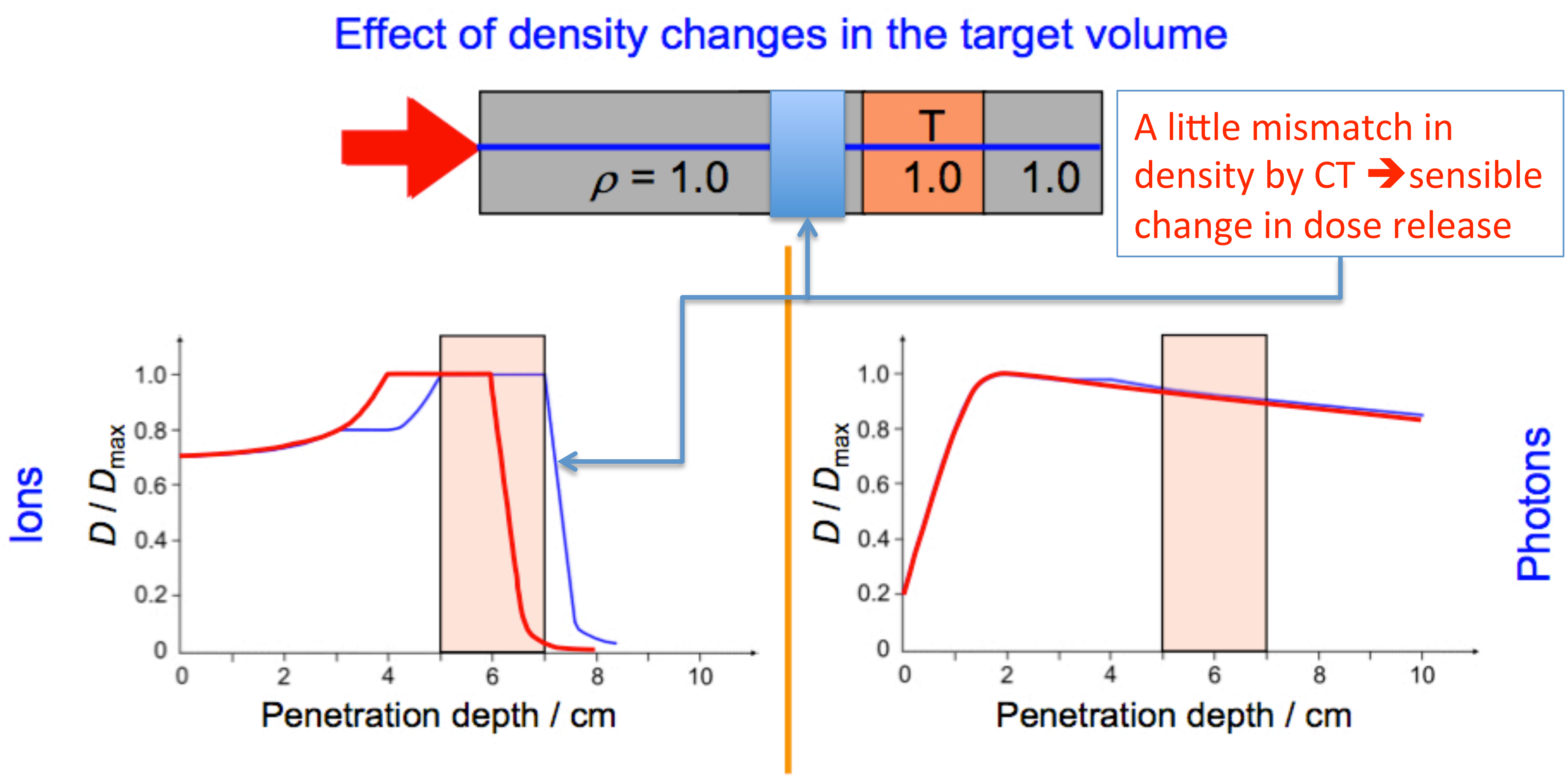
Total for all facilities (in operation and out of operation):

2054	He
1100	pions
7151	C-ions
873	other ions
67097	protons
78275	**Grand Total**

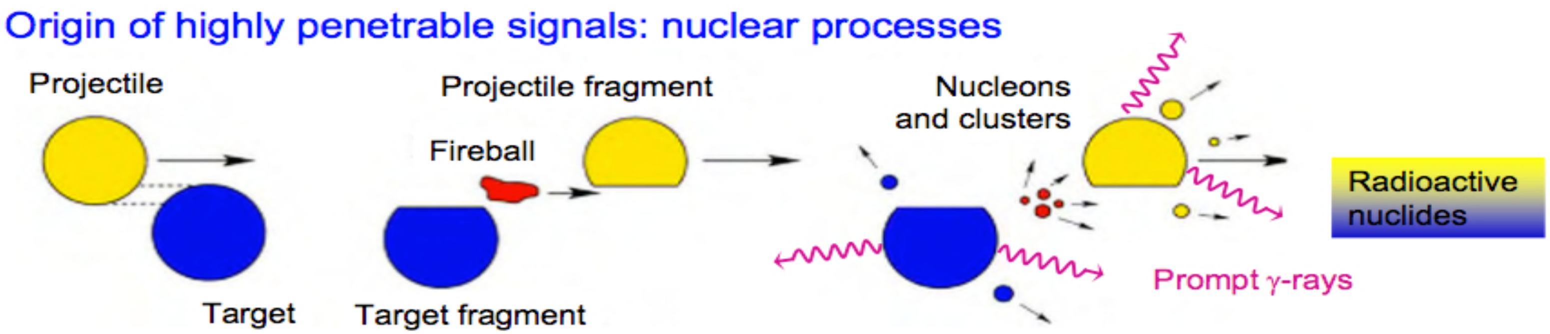
Particle Therapy Co-Operative Group

Monitoring the dose

- Why is so crucial to monitor the dose in hadrontherapy ? Is like firing with machine-gun or using a precision rifle..



Spec's of hadrontherapy monitor



- Measure shape and absolute value of dose to check the agreement between the planned target volume and the actually irradiated volume
- The measurement should be done during the treatment (in-beam)
- Must rely on a given secondaries generated by the beam that comes out from the patient, to spot the position of the dose release
- Must be able to deal with the other secondaries that come out that acts like background

baseline dose monitoring in HT : PET

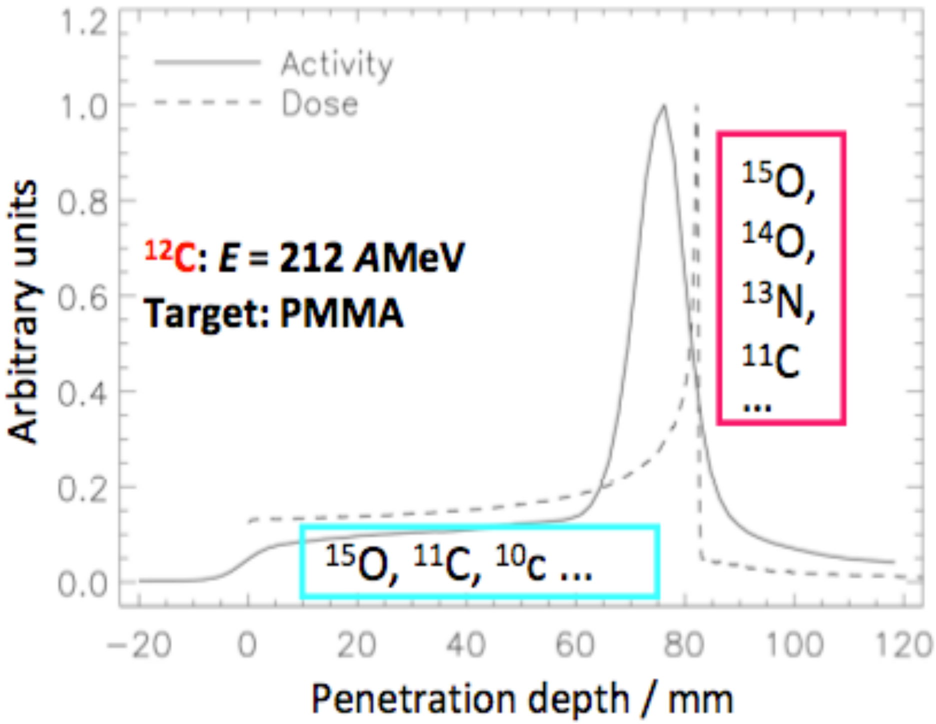
Baseline for monitor in HT is PET : autoactivation by p & ^{12}C beam that creates β^+ emitters.

- Isotopes of short lifetime ^{11}C (20 min), ^{15}O (2 min), ^{10}C (20 s) wrt conventional PET (hours)
- Low activity in comparison to conventional PET need quite long acquisition time (few minutes)
- Metabolic wash-out, the β^+ emitters are blurred by the patient metabolism
- No direct space correlation between β^+ activity and dose release (but can be reliable computed by MC)

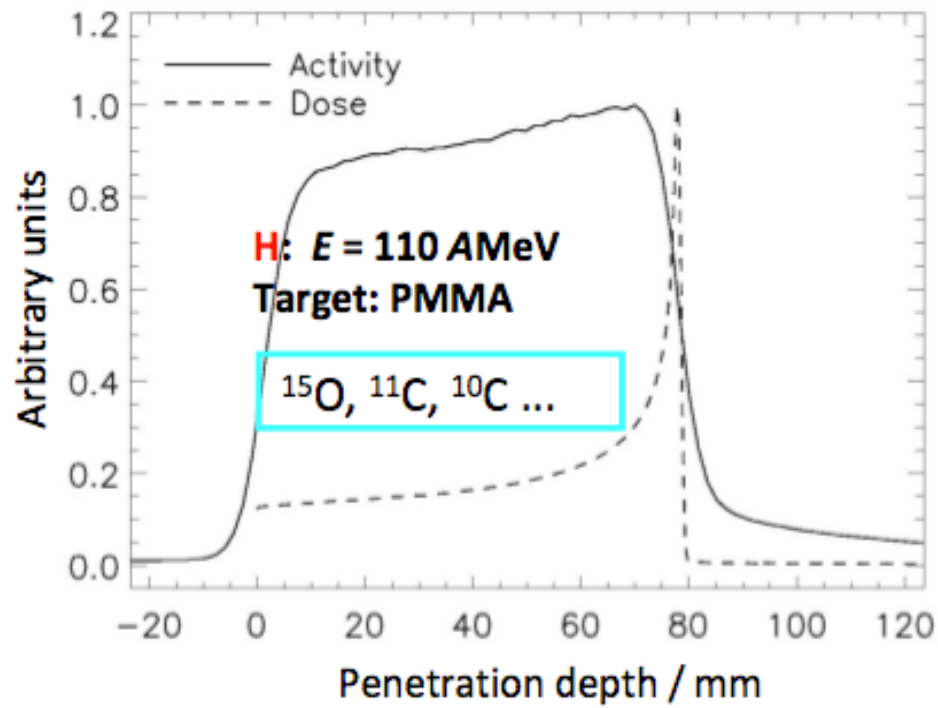
Correlation between β^+ activity and dose

Therapy beam	^{1}H	^{3}He	^{7}Li	^{12}C	^{16}O	Nuclear medicine
Activity density / Bq cm^{-3} Gy^{-1}	6600	5300	3060	1600	1030	$10^4 - 10^5$ Bq cm^{-3}

Projectiles & target fragmentation



Target fragmentation

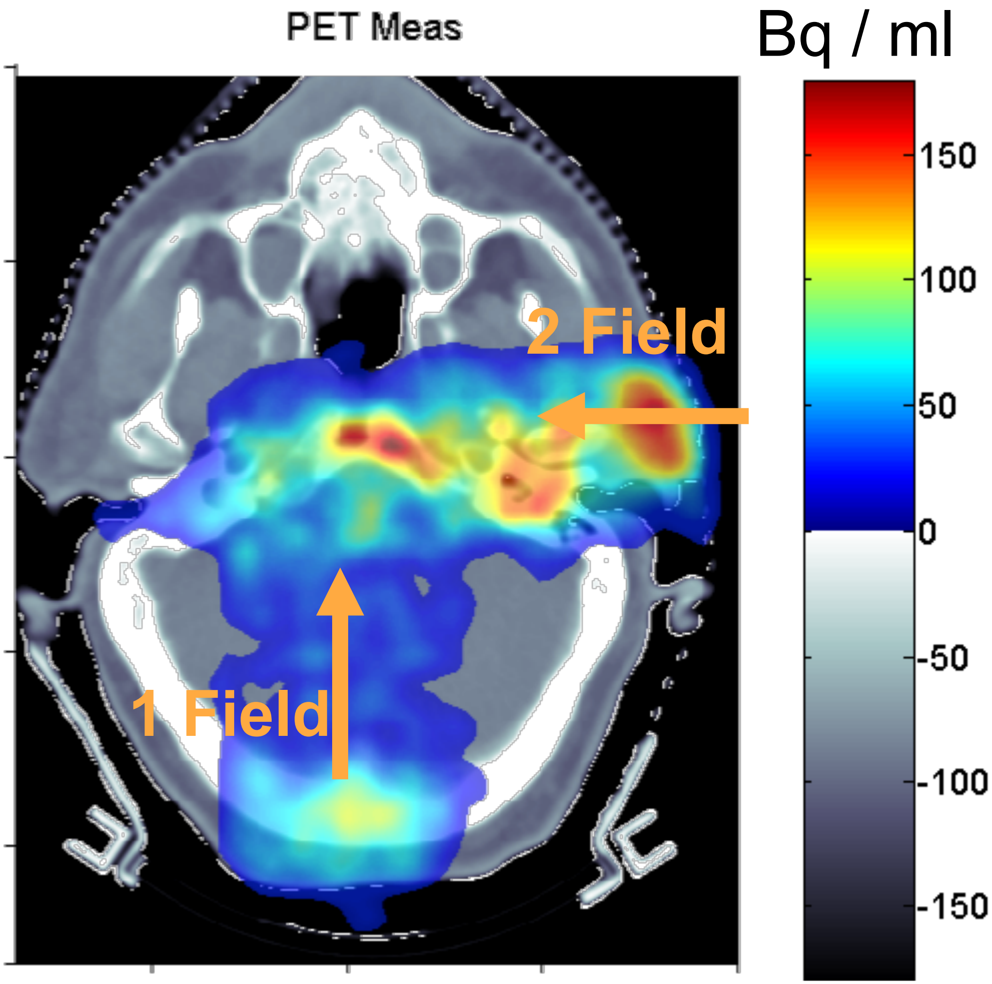


Post-radiation PET/CT @ MGH

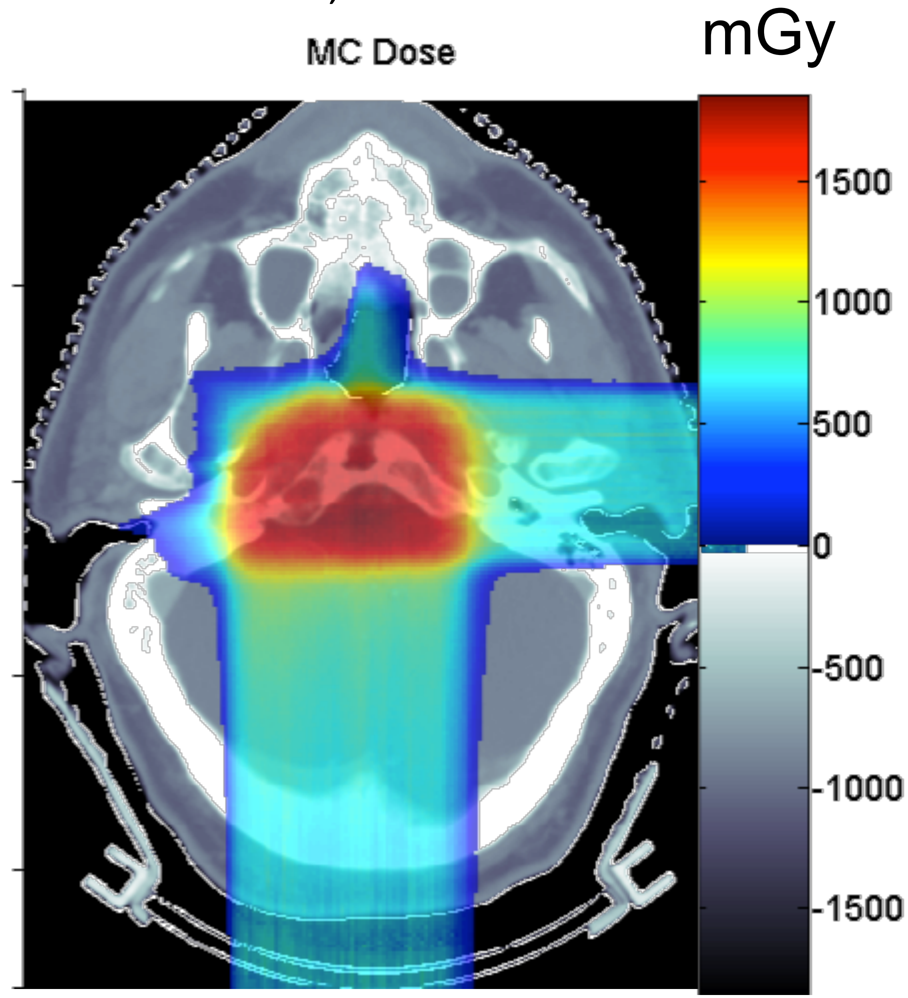
PROTON BEAM: conventional PET-CT

Clival Chordoma, 0.96 GyE / field,

ΔT1 ~ 26 min, ΔT2 ~ 16 min



Average Activity

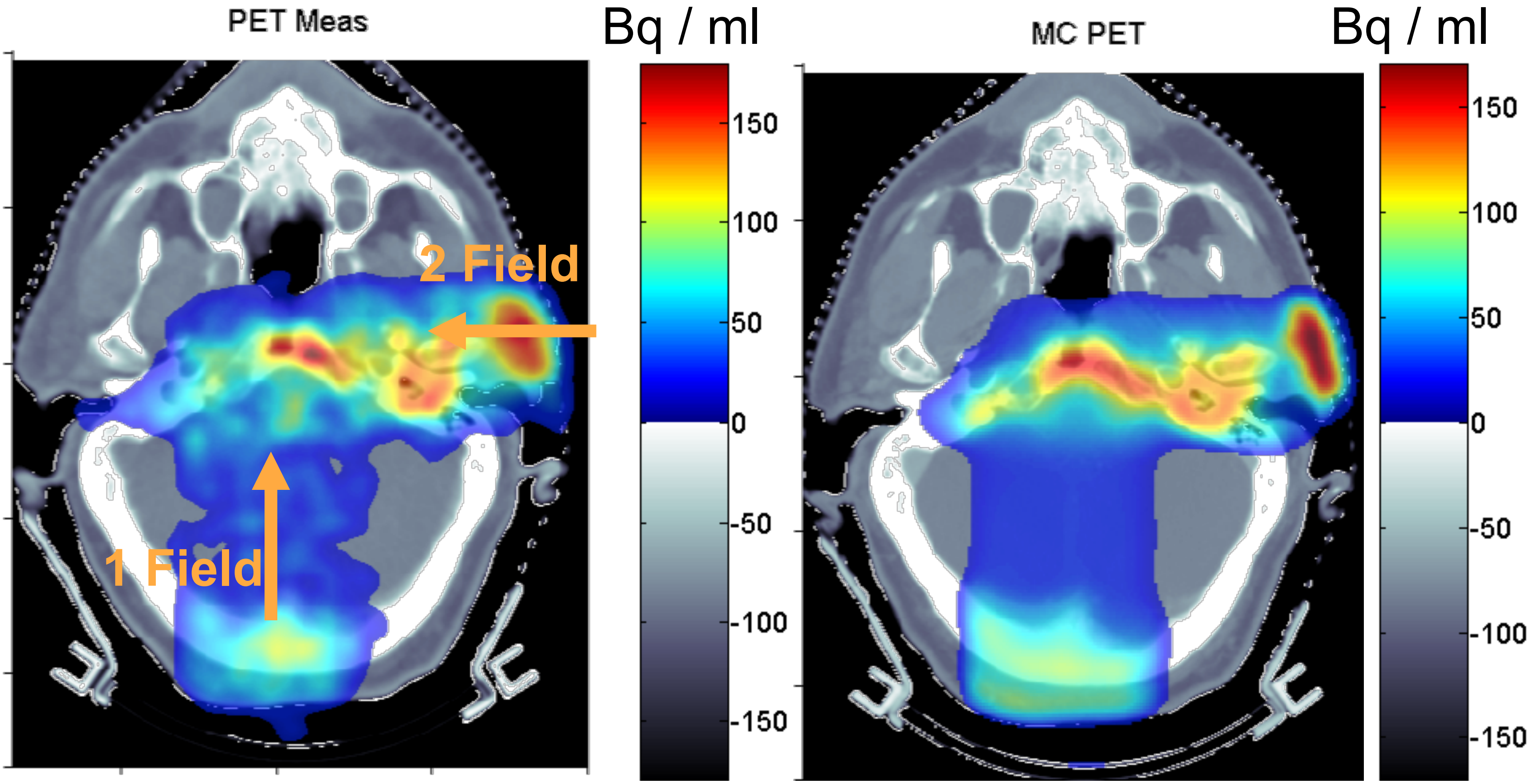


K. Parodi et al, IJROBP 2007

Planned dose

Post-radiation PET/CT @ MGH

Clival Chordoma, 0.96 GyE / field, ΔT1 ~ 26 min, ΔT2 ~ 16 min



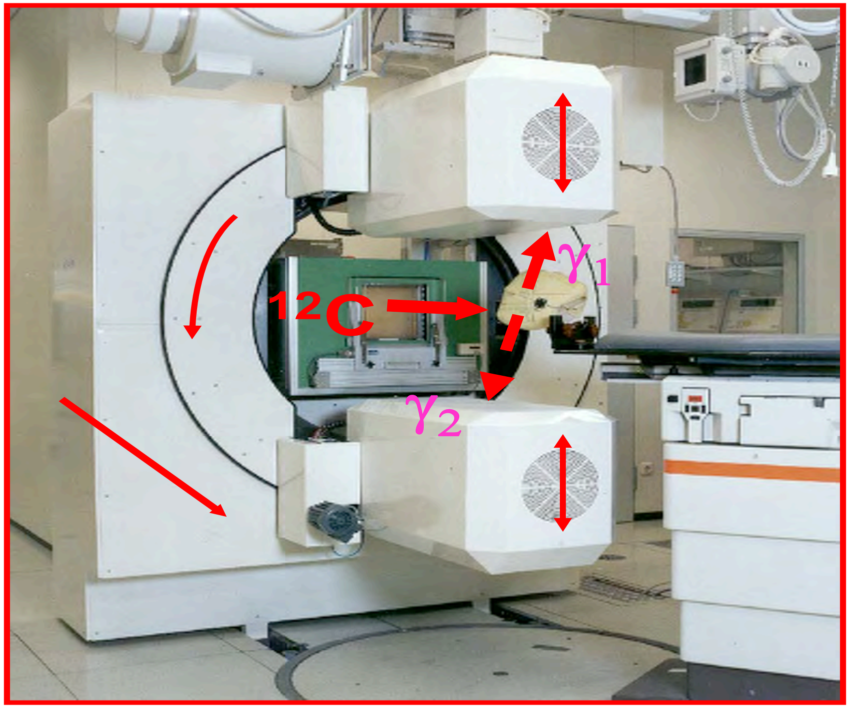
Average Activity

K. Parodi et al, IJROBP 2007

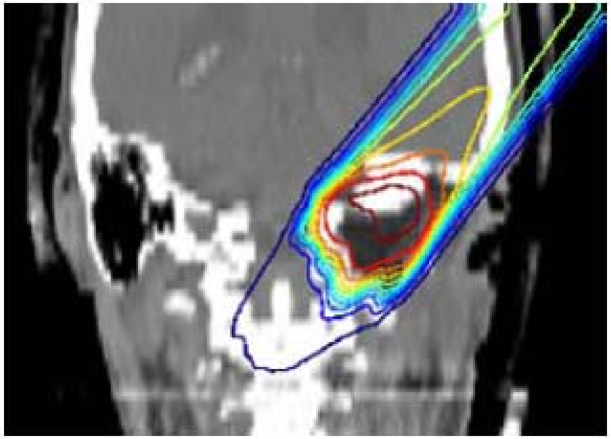
In -beam PET @GSI

CARBON BEAM: 2 heads x 64 crystals

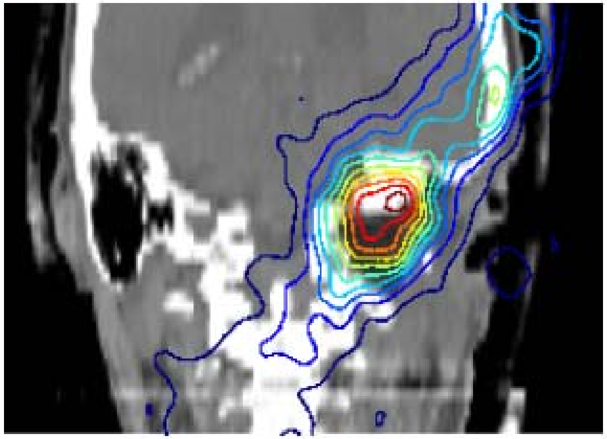
- Less acceptance
- No patient movement
- Less methabolic washout
- Background from the beam



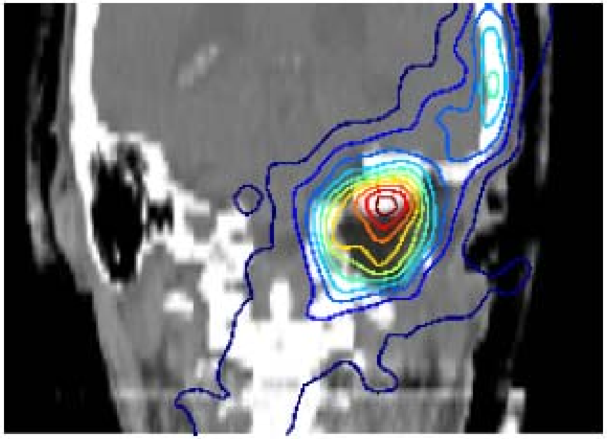
279, W. Enghardt et al.: Nucl. Instr. Meth. A525 (2



Treatment plan



Predicted β^+-activity



Measured β^+-activity

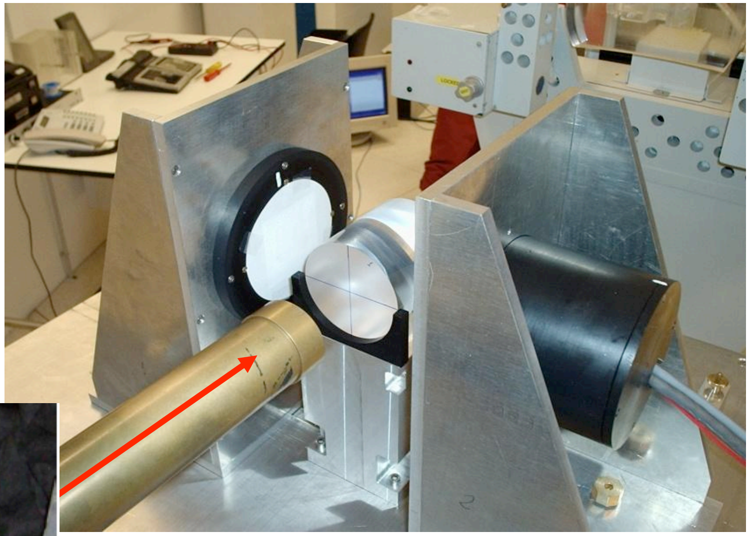
A dedicate PET: the DO-PET project

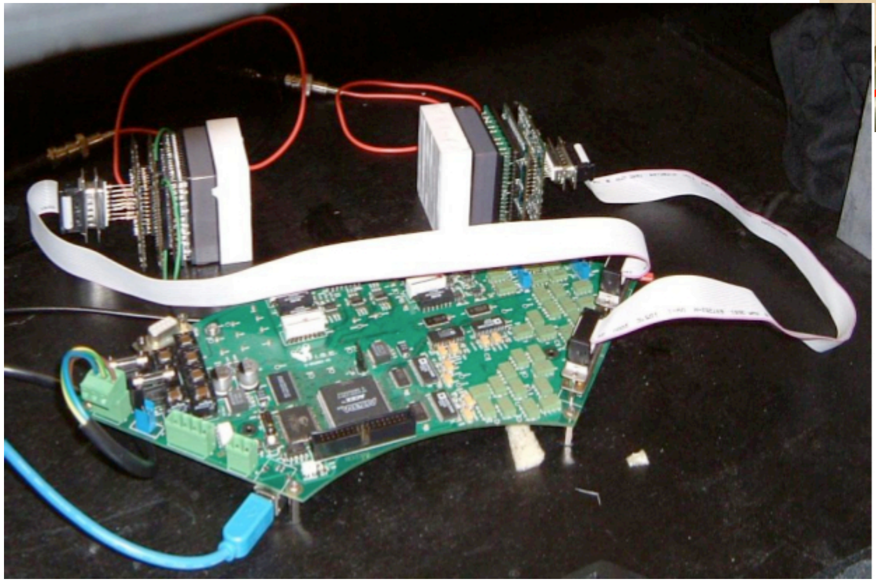
Scintillating crystals LYSO:Ce from Hilger

PS-PMT H8500 from Hamamatsu Photonics K.K.:

F.Attanasi @ IFA 2010

- Homogeneous cylindrical phantoms of PMMA at center of FoV;
- Spread-out Bragg Peak (SOBP, 10.8 mm plateau width) irradiation;
- Delivered dose: 30 Gy;
- Irradiation Time: ~60 s;

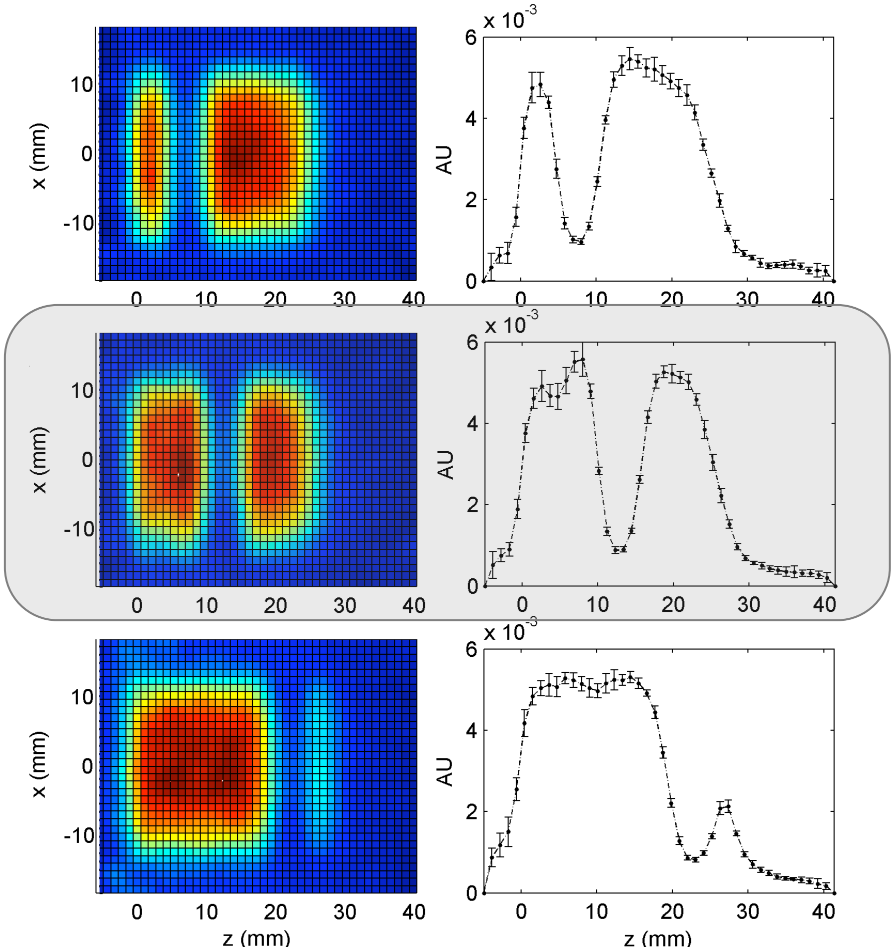




- Final collimator: 25 mm Ø;
- Distance between detectors:14 cm.
- PET acquisition time:20 min.
- FoV: 42 x 42 x 42 voxels.
- 1.076 x 1.076 x 1.076 voxel dimension.

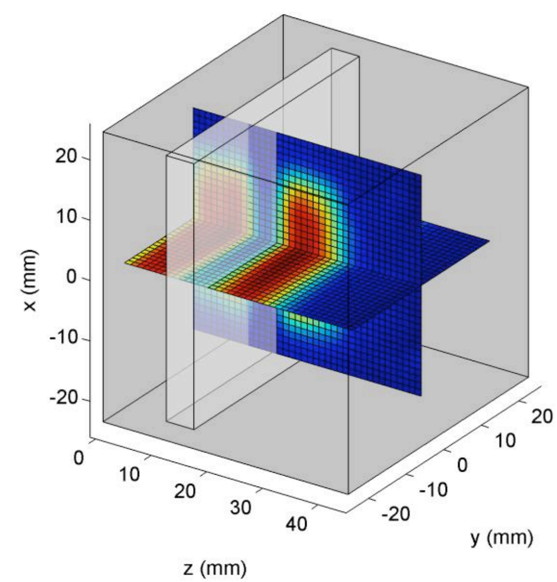
The DO-PET prototype

PMMA phantoms with 0.5 cm Air_Gap at different depth;



OFF beam PET : long acquisition time

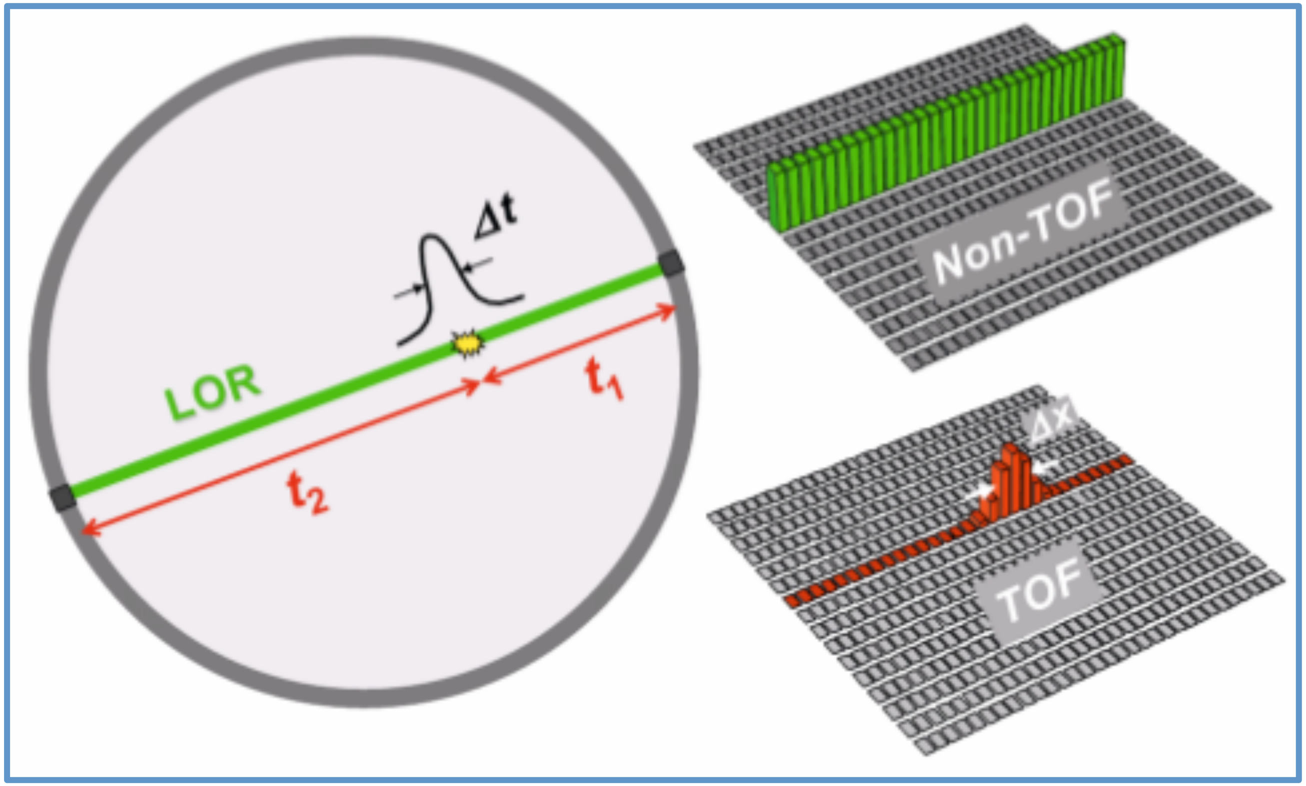
- Phantom irradiations:
  - Bragg peak dose: 30 Gy
  - Irradiation time: 18 s;
- Beam cross sention: 2.5 cm Ø;
- Acquisition time: 20 min;



Going further: in-beam TOF-PET

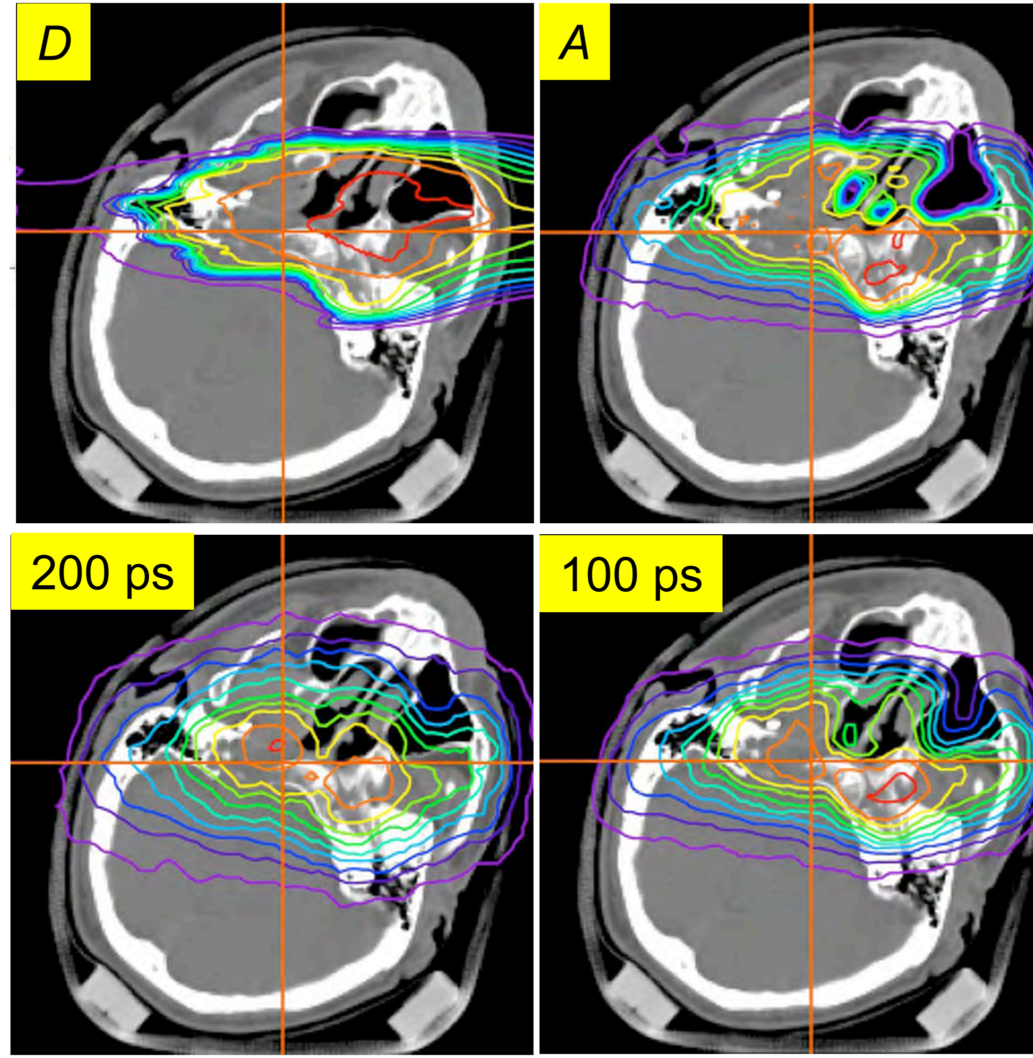
Improving the reconstruction and reducing background using the time difference between the Time Of Flights of the 2 collinear γ

- Improvement in the S/B ratio
- Better accuracy with less statistic
- Easier events reconstruction
- O(200ps) time resolution on 511 keV γ needed



The goal: real time monitoring by ToF-PET

- On line feedback to the accelerator
- From the activity monitored on line during the treatment to the istantaneous (minutes) dose delivered
- R&D on crystals, PMTs, electronics to go for σ_{TOF} ~100ps (3 cm space res)
- Negligible background



P. Crespo et al., Phys. Med. Biol. 52 (2007) 6795

Background or Signal?

Balance of promptly emitted particles outside the target:

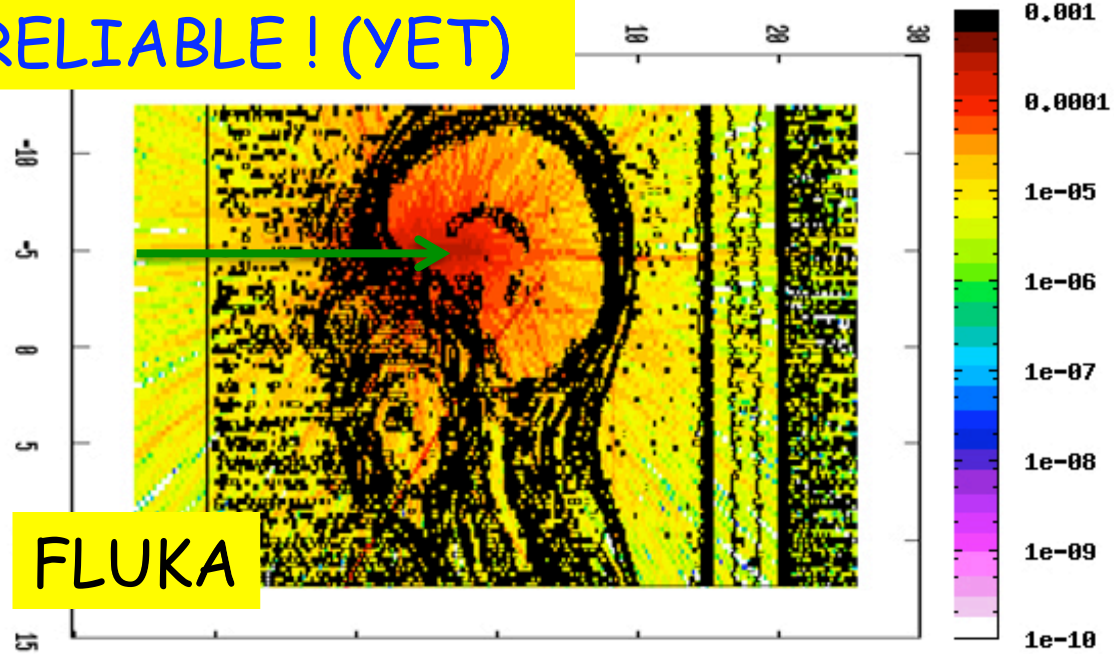
G4

Incident protons:	1.0	($\sim 10^{10}$)
γ-rays:	0.3	($3 \cdot 10^{9}$)
Neutrons:	0.09	($9 \cdot 10^{8}$)
Protons:	0.001	($1 \cdot 10^{7}$)
α-particles:	$2 \cdot 10^{-5}$	($2 \cdot 10^{5}$)

The p, ^{12}C beams generate a huge amount of secondaries.. expecially prompt single γs. and neutrons in the 1-10 MeV range. Can be used to track the beam inside the patient

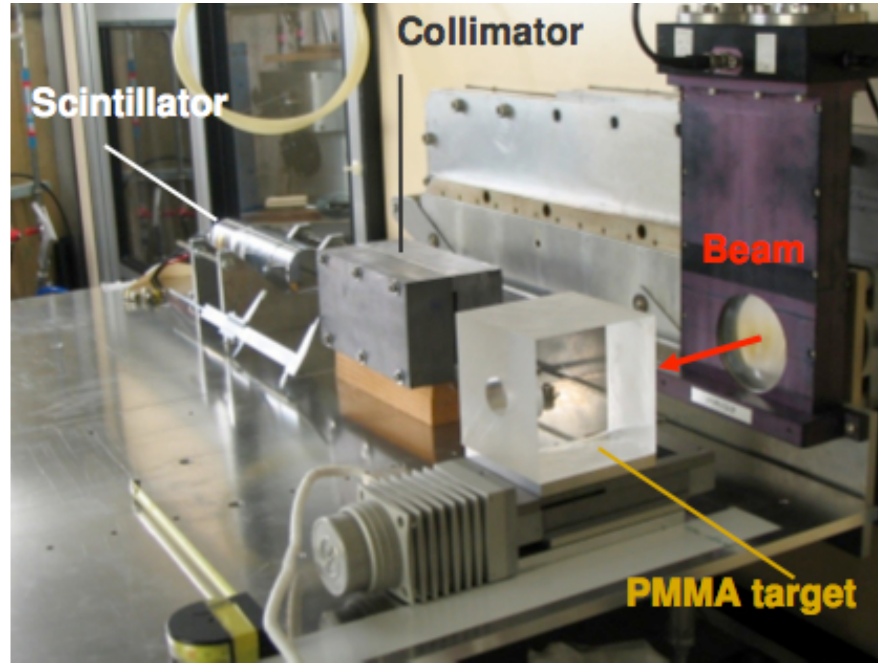
NOT RELIABLE ! (YET)

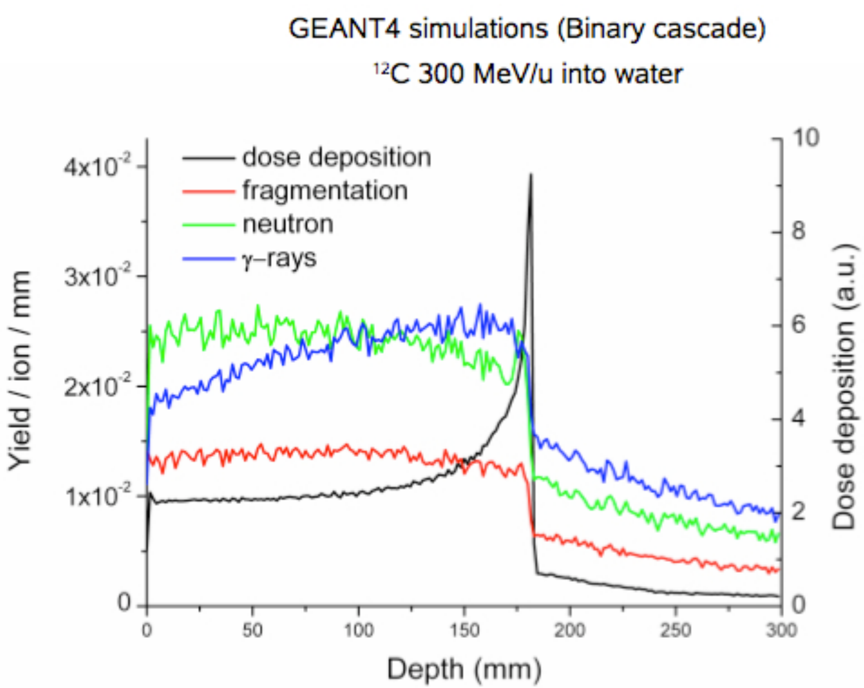
The nuclear models inside MC (FLUKA&G4) not yet able to fully describe this physics ➔ huge development effort ongoing

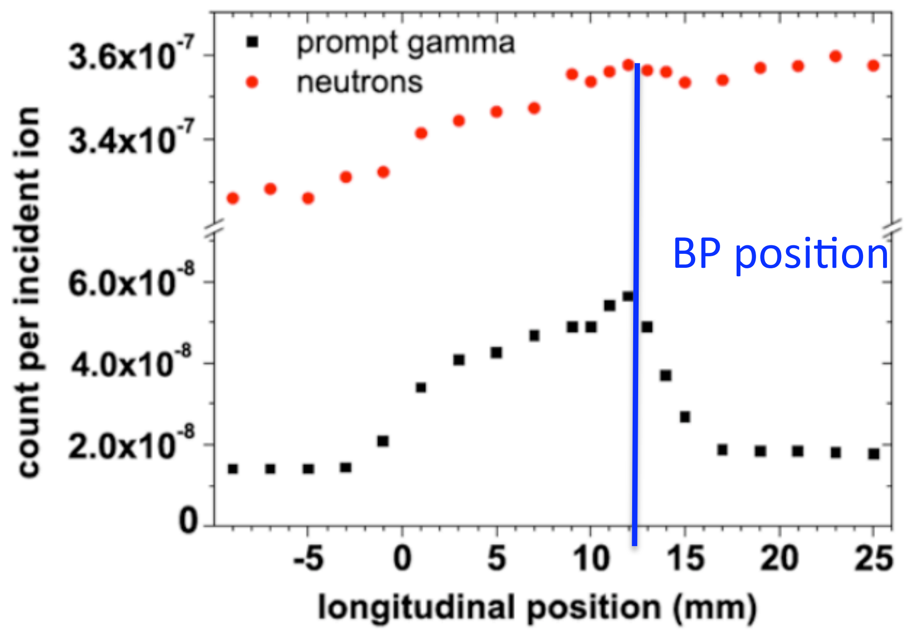


Prompt γs @GANIL

- 73 AMeV carbon beam
- γ peak correlated with BP
- MC one order of magnitude off (more..)
- Neutrons background (TOF rejection ?)



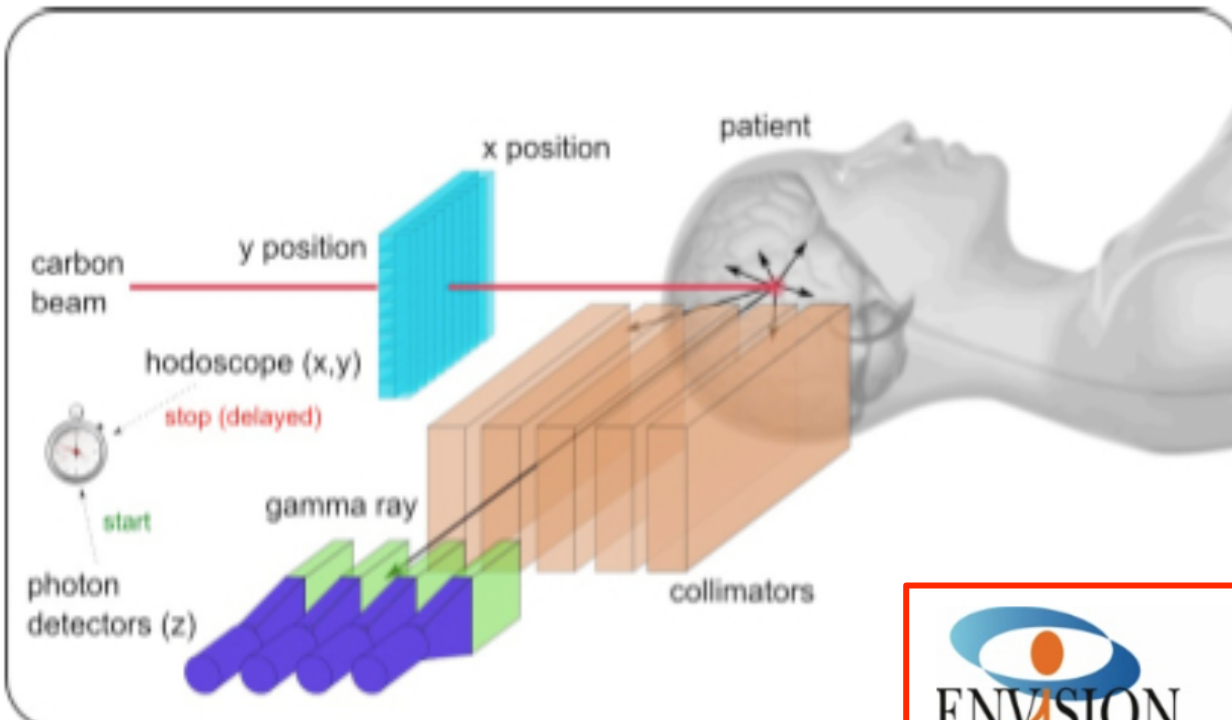




Possible prompt γ monitoring: Gamma camera

- Large flux, maybe enough stats for in-beam
- Collimation like Anger camera in SPECT
- Well known technique, robust, compact

- Wide γ energy spectrum → careful design
- Neutron background rejection? TOF not so easy to exploit.
- Collimation reduces stats



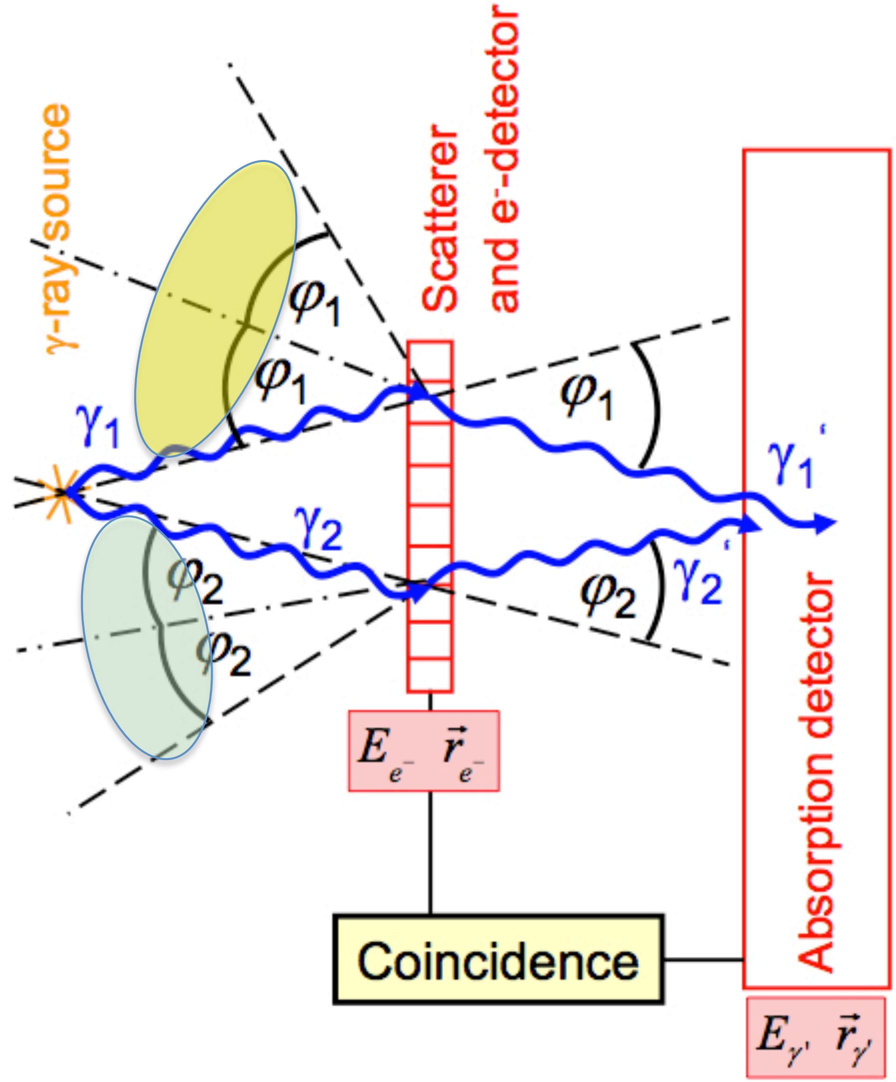
ENVISION

More sophisticated… Compton Camera

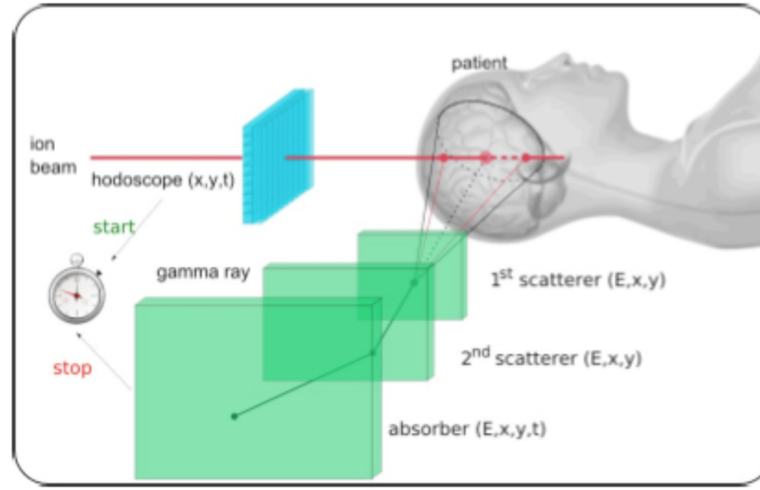
$$\cos\varphi = 1 - m_0 c^2 \left(\frac{1}{E_{\gamma'}} - \frac{1}{E_\gamma} \right)$$

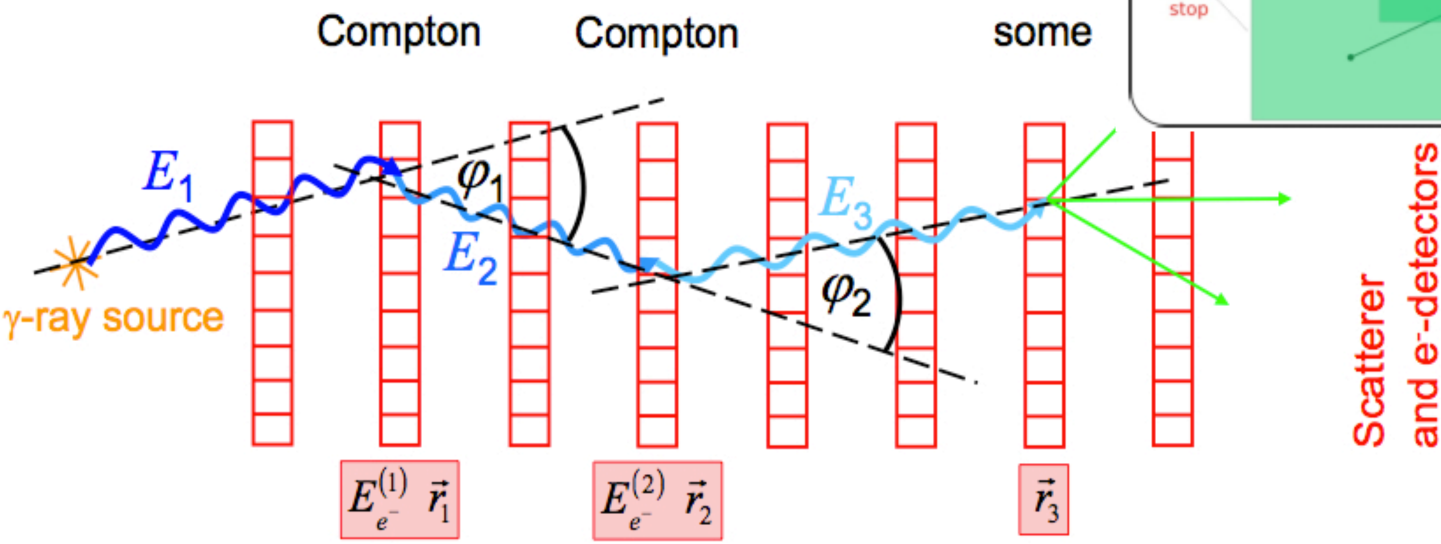
Based on γ Compton scattering: known E_γ, measure $E_{\gamma'}$, $\mathbf{r}_\gamma$, $\mathbf{r}_{\gamma'}$ ➔ obtain f. But…

- E_γ not fixed ➔ continuous γ spectra
- γ′ must be completely absorbed in the second detector



Even More sophisticated… Multiple Compton Camera





$$\cos\varphi_1 = 1 - m_0c^2\left(\frac{1}{E_2} - \frac{1}{E_1}\right)$$

$$\cos\varphi_2 = 1 - m_0c^2\left(\frac{1}{E_3} - \frac{1}{E_2}\right)$$

$$E_{e^-}^{(1)} = E_1 - E_2$$

$$E_{e^-}^{(2)} = E_2 - E_3$$

Known : $\varphi_2, E_{e^-}^{(1)}, E_{e^-}^{(2)}$

Unknown : $\varphi_1, E_1,$ E_2, E_3

- Efficiency: 25 – 50 % for E_1 > 1 MeV
- No absorption necessary
- No high Z absorber required

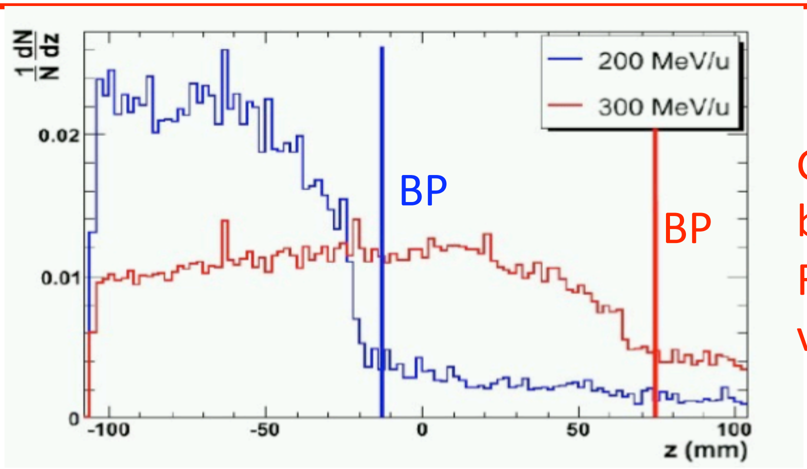
Spatial resolution is an issue!

Neutron background?

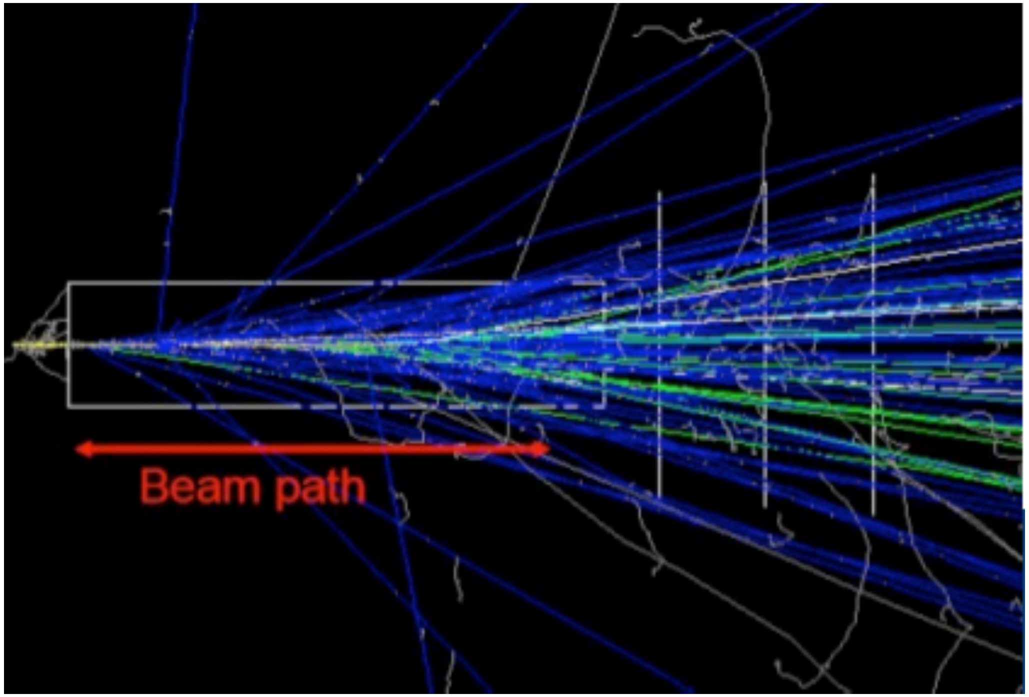
J.D. Kurfess et al., 5th Compton Symposium, Portsmouth, New Hampshire, AIP Conference Proceedings, 1999

Diving in the future… the charged signal!

- Low energy p emitted also near BP (Fermi motion). Enough energy to be useful?
- Best space resolution for large angle emission → low statistic
- MC highly unreliable, probing the very tail of the angular distribution of secondary



G4 : proton beam. Reconstructed vertex

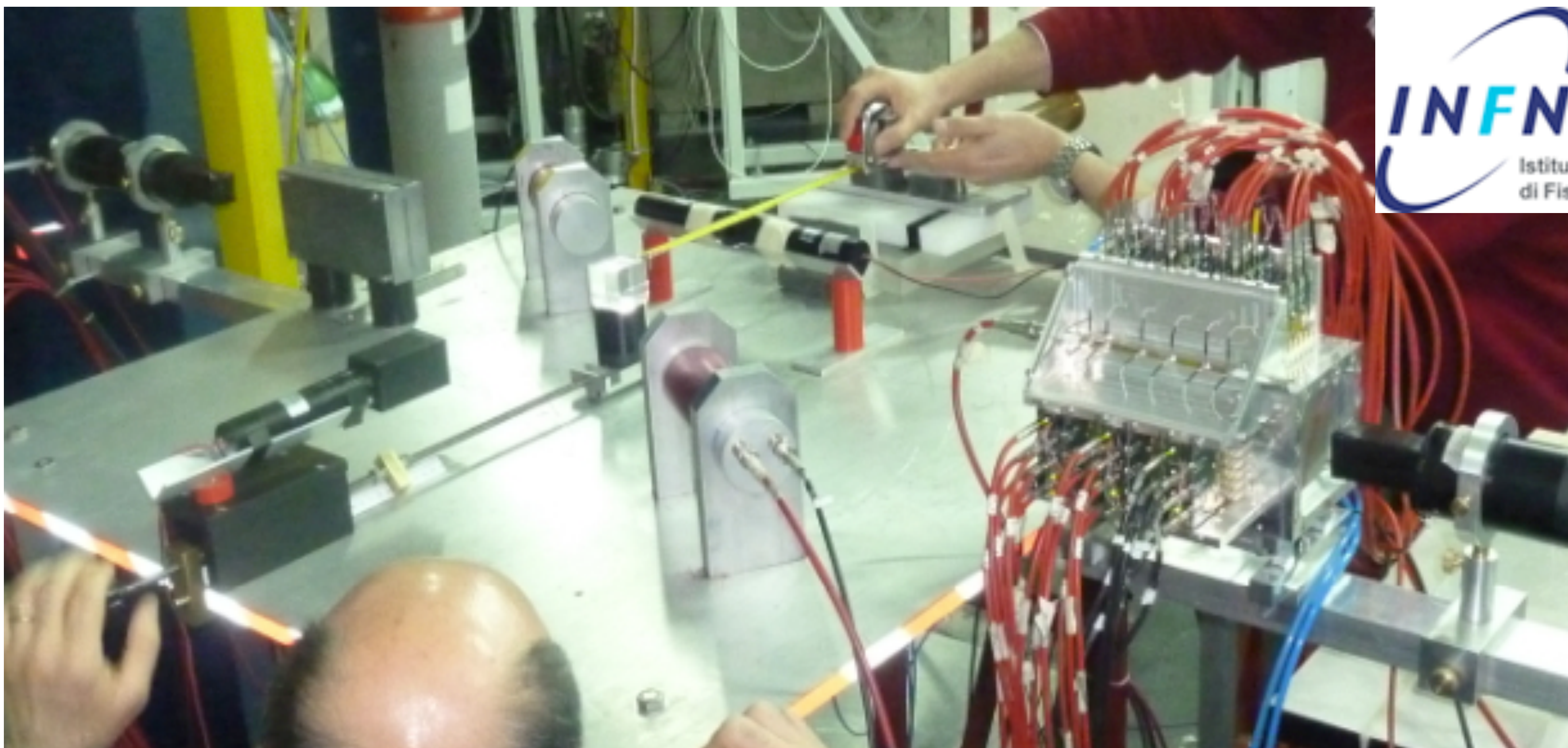


Envision WP2 2011 Report

Coming back to reality: flux measurement…

RM1, LNF,LNS : Measurement of β^+, γ, p, n & charged sec fluxes induced by the ^{12}C 80AMeV @LNS on PMMA phantom

NAI counter → β^+ ; LYSO counter→ γ,n ; Drift Chamber→Charged ; PLASTIC counter→low angle frags

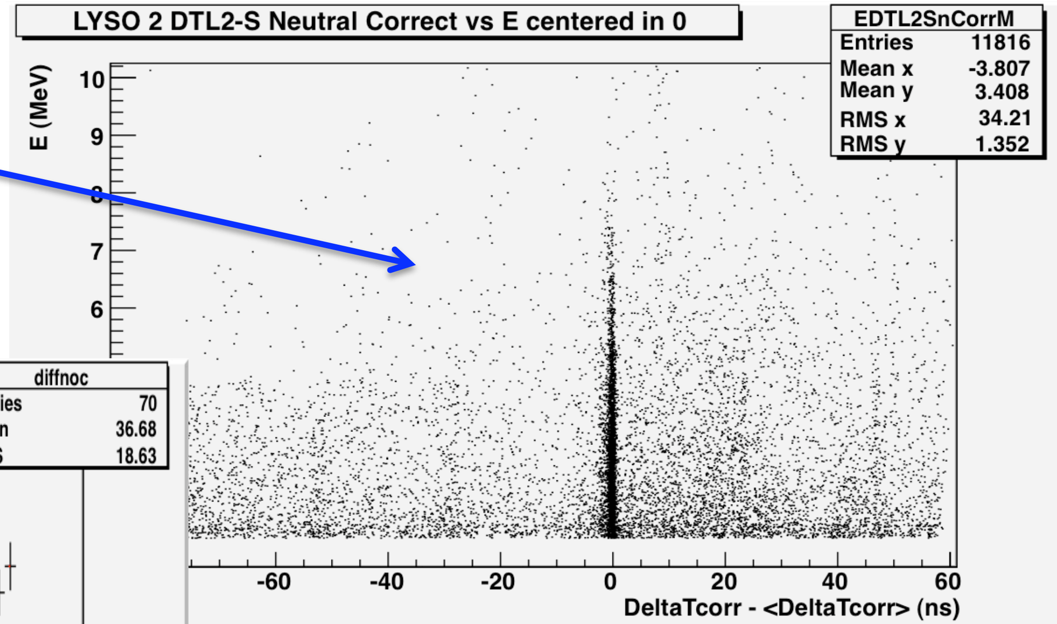


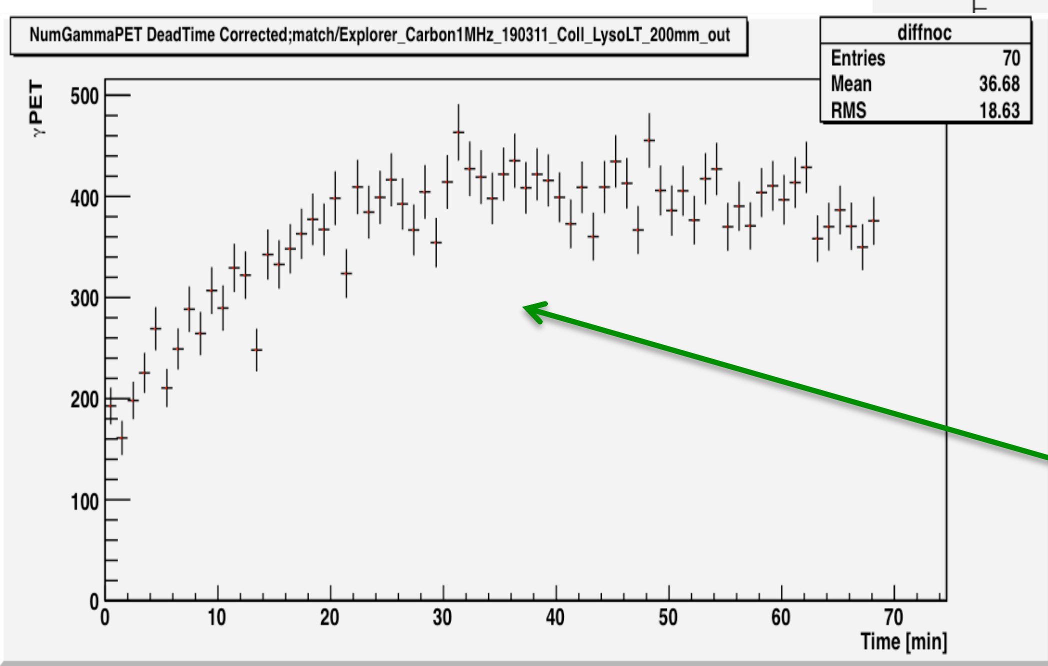
INFN Istituto Nazionale di Fisica Nucleare

Work in progress…

This measurement campaign is a prerequisite to the design phase of HT monitor device

Energy vs TOF distribution in LYSO counter at 90^0. Clearly seen the prompt γ signal and n background





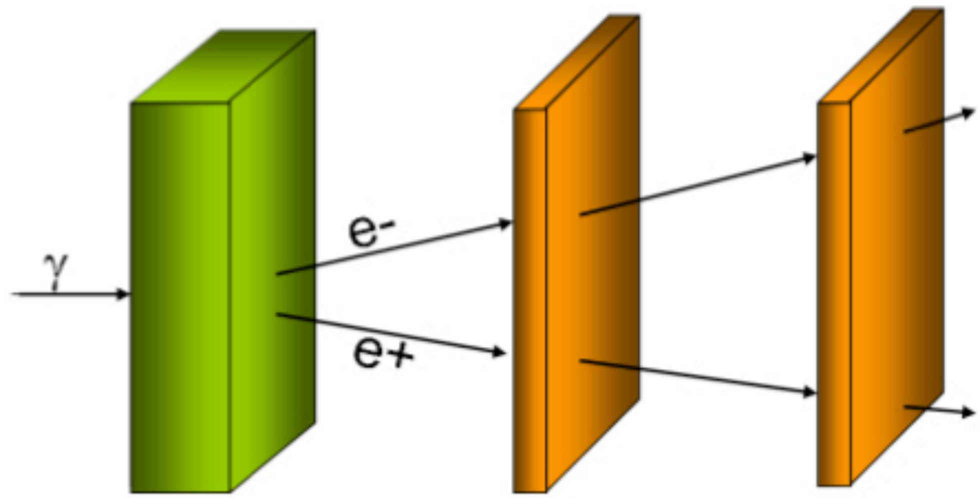
β+ activity of the phantom at the beam start as detected by the NAI couple. Loading up to a "secular" equilibrium.

Summary & conclusions

- Hadrontherapy is an established therapy with increasing spread in the word
- There is a common need for reliable, precise and compact monitor devices
- INFN has a huge activity in the field, spread out in several sites on accelerators, software (Treatment Planning System) and monitor devices (also in collaboration with companies like IBA)
- There is plenty of work to be done…

Spare slides

The Pair Camera



Tasks:

- Simulation with Geant4
- Optimize setup:
  - ➢ Target and detector material
  - ➢ Target and detector dimensions
- Combination with Compton Camera
- Accuracy of source localisation, spatial resolution

Known problems from pairproduction camera in astronomy:

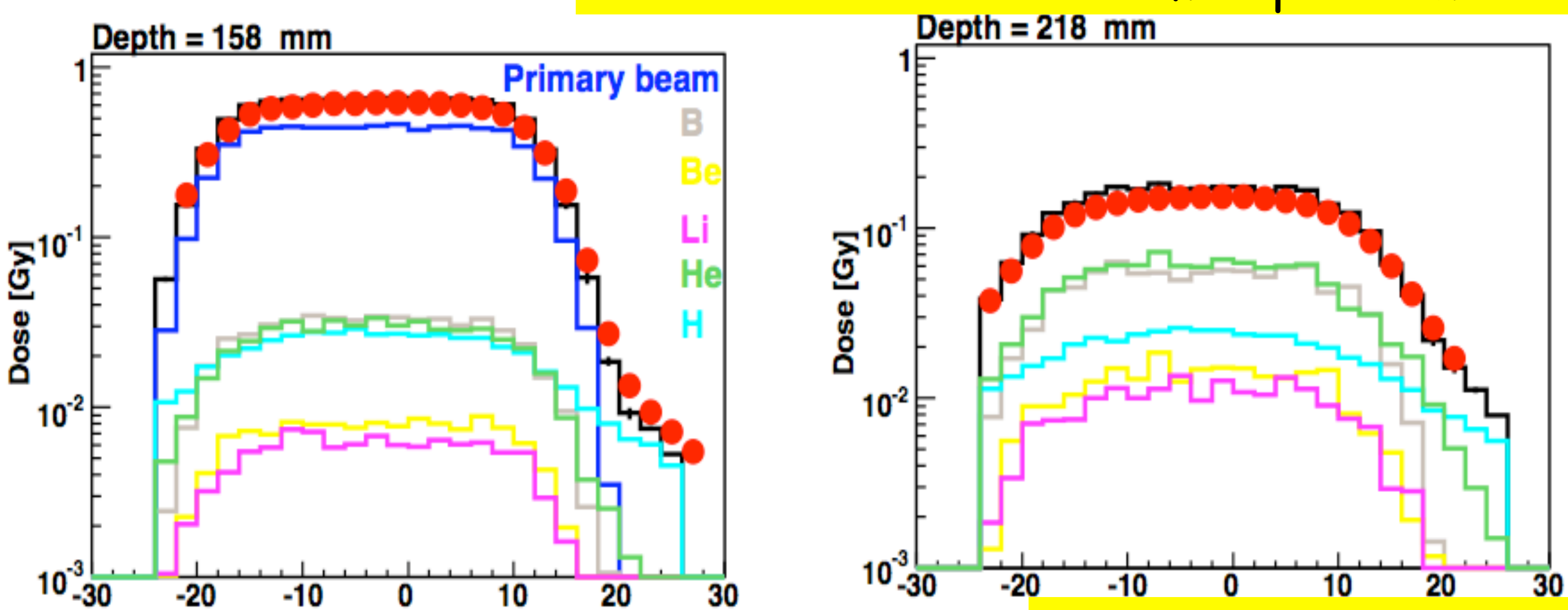
- Recoil of nuclei: uncalculable changes of angles
- Coulomb scattering of electron and positron

➡ Decision if useful for in-beam SPECT

FRAGMENTATION OF CARBON IONS

The secondary fragments, especially the lighter ones such H and He, broad the lateral dose profile.
Effect gets more and more important approaching, and going beyond, the Bragg Peak i.e. the tumor region

SOBP centered al 20 cm depht in water



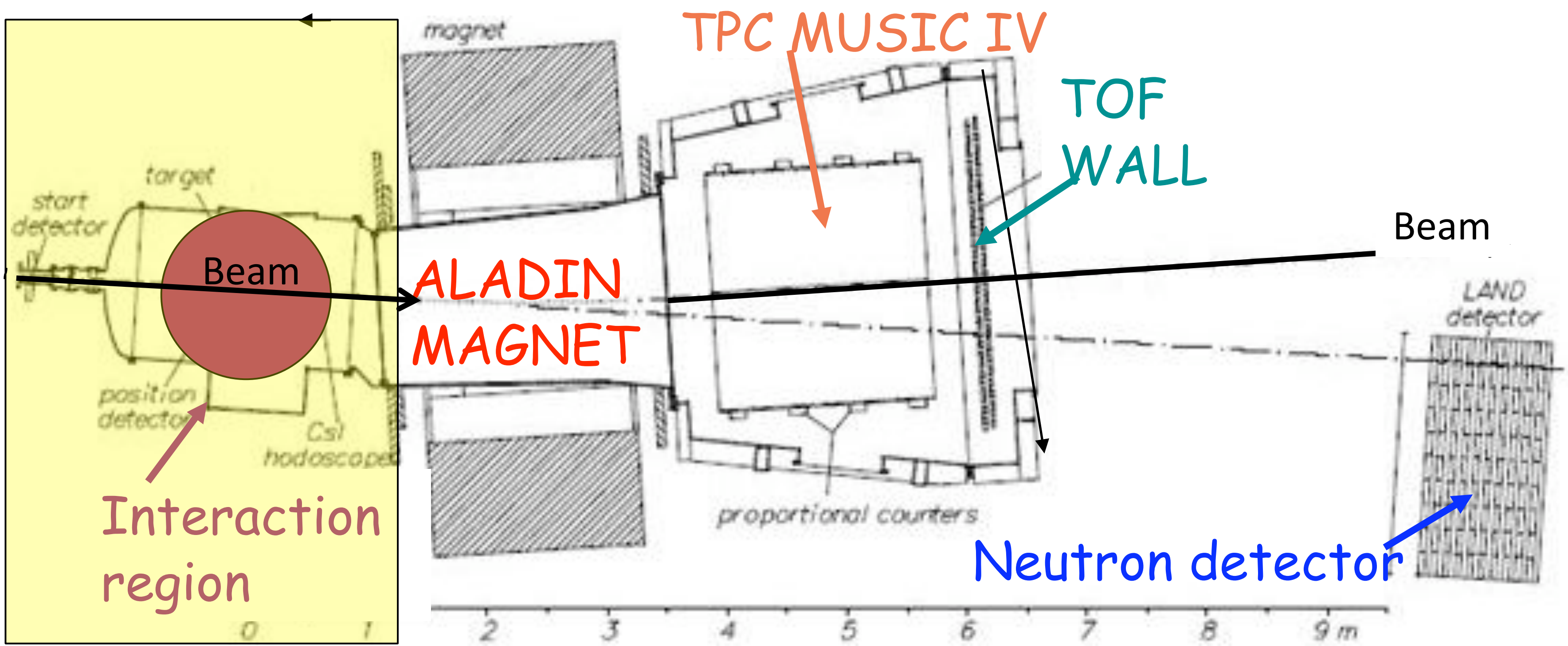
Lateral displacement(mm)

Lateral displacement(mm)

Data: S. Brons & K. Parodi (GSI)
MC-FLUKA: A. Mairani PhD Thesis 2007 Pavia

The ALADIN setup @GSI

- The choice of GSI has 2 main motivations:
  - ✓ "Terapeutical" beam of ^{12}C @ 200-400 MeV/u available
  - ✓ Existing setup designed for higher E and Z fragments: Dipole magnet, Large Volume TPC, TOF Wall, low angle Neutron detector.
- New detectors added to optimize the Interaction Region for this measure: Vertex tracker, Start Counter, Beam Monitor, Proton Tagger



Radiotherapy and secondary cancers

Cancer survivors represent about 3.5% of US population

Second primary malignancies in this high-risk group accounts for about 16% of all cancers

Three possible causes:

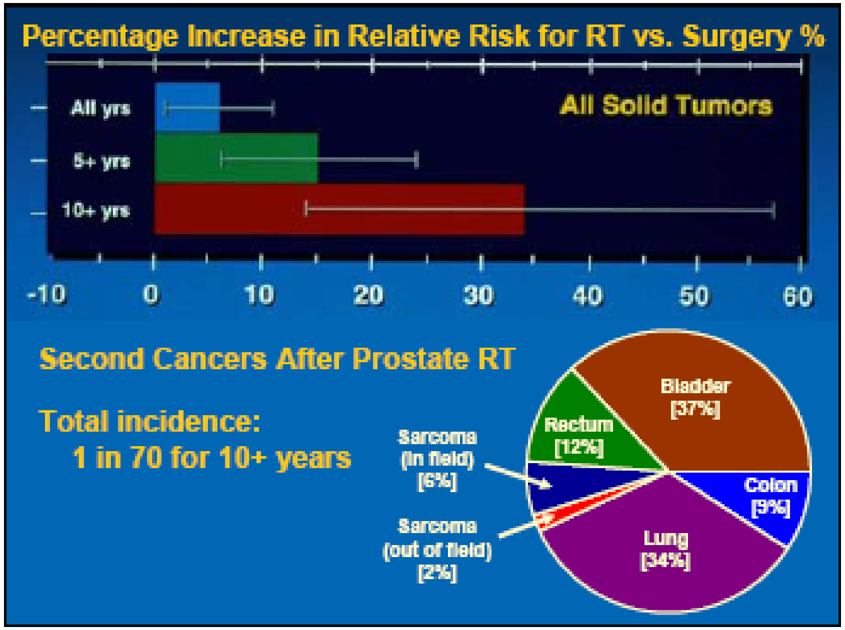
- Continuing lifestyle
- Genetic predisposition
- <u>Treatment of the primary cancer</u>

Assessment is difficult because of lack of controls

Prostate and cervix cancer: surgery is an alternative

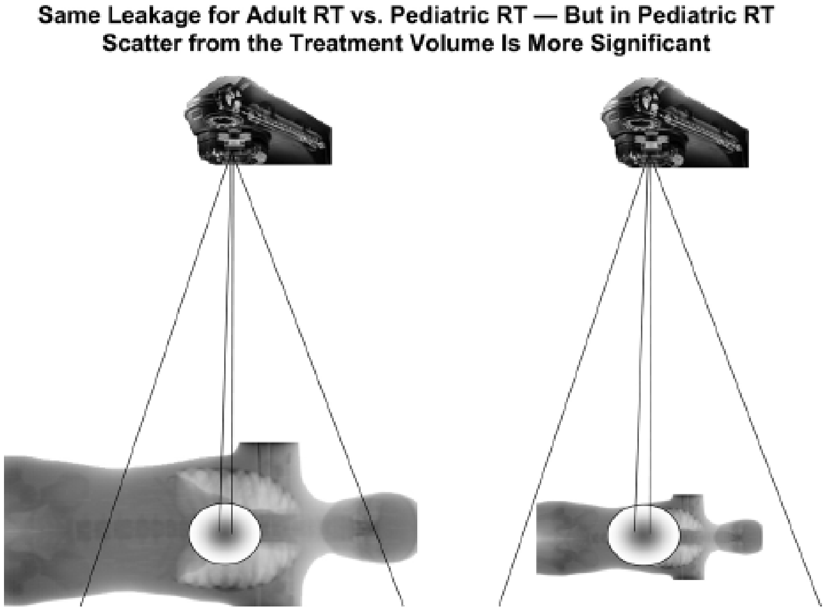
Hodgkin's lymphoma: risk of breast cancer very high

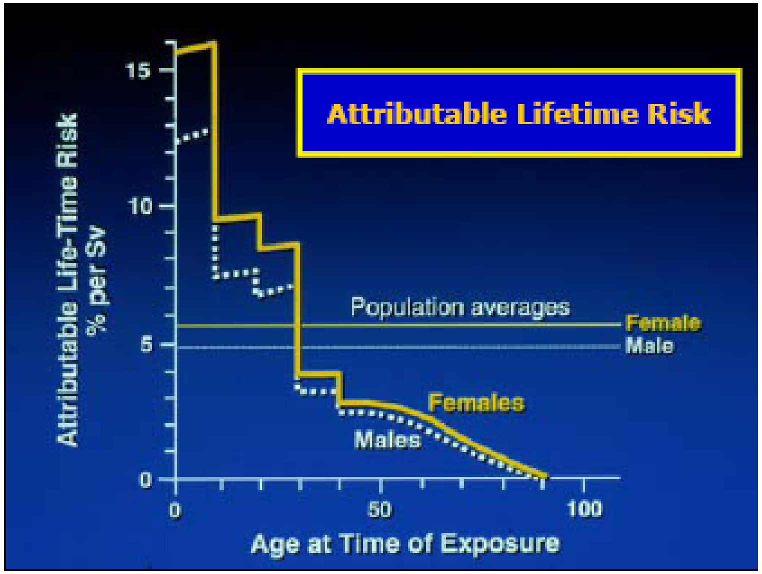
Radiation-induced secondary cancers are mostly carcinomas, but a sarcomas in heavily irradiated sites are also observed



Brenner *et al.*, *Cancer* (2000)

Pediatric patients





Hall, *IJROBP* 2006

Work in progress

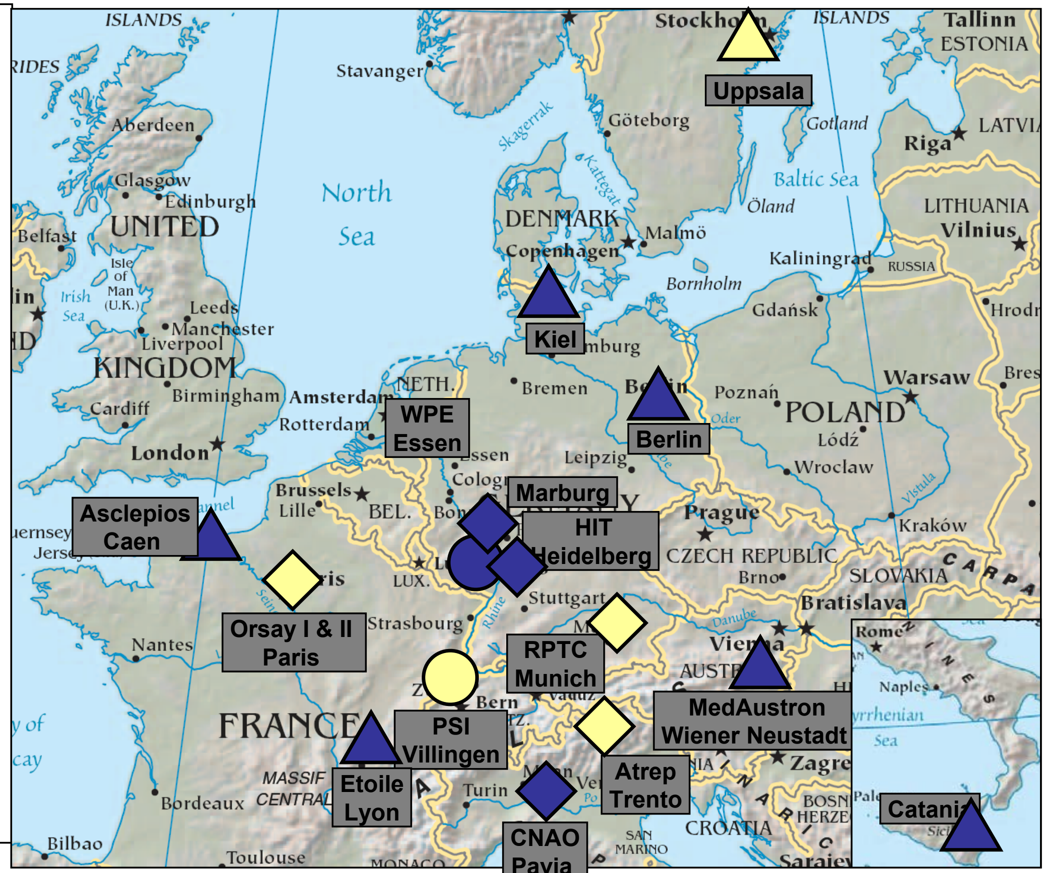
Future developments for C-ion therapy

GSI 1997-2008 (over 400 patients treated)

Heidelberg: first RT 2009

Pavia : first RT 2010

Marburg , Kiel, Wiener Neustadt , Lyon, .



The "standard" paradigm

1 Gy γ-rays in one nucleus:

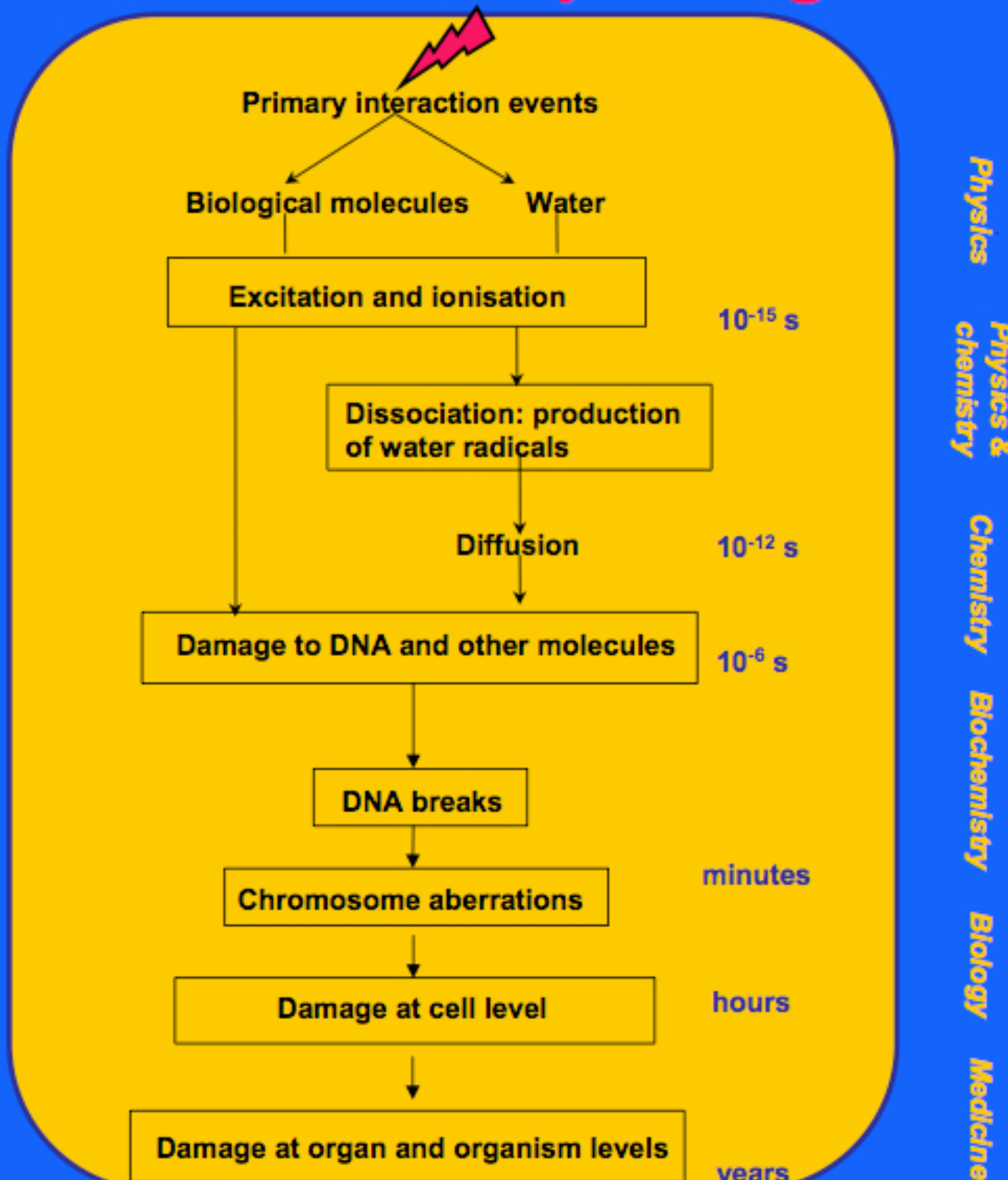
≈ 100,000 ionizations
(≈ 2,000 in the DNA)

≈ 40 DNA DSBs,
≈-1 "complex lesion"

≈ 0.5-1 chromosome aberrations

≈ 0.5-1 lethal lesions
≈ 10^{-5} HPRT mutations
≈ 10^{-5} neoplastic transformations

<< 10^{-5} cancers



Other Paradigms:
Instabilty;
Bystander;
Micro-environment;
Inflamation;
etc ....

Increased need for Radiotherapy

-one cancer out of two needs RXT

- <u>Population increase</u> : 2020 : 8 Billions in the world

  (300/100.000) : 24 millions cancer/year

  12 millions RXT : 24.000 linacs (1/500 patients)

- <u>Population ageing</u> : 2010-2030

  people above 65yx2

  people above 80yx3 (surgery ↘)

- <u>Metastatic chronic phase</u> : RXT ↗

  Oligo meta : brain – lung – liver etc …