Hadron therapy for cancer treatment

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Outline

- Introduction
- Brief History of Hadron Therapy
- Radiotherapy effects
    - Photons
    - Protons
    - Heavy Ions
- The situation in the world and in Italy
- CNAO
- Conclusions

Introduction

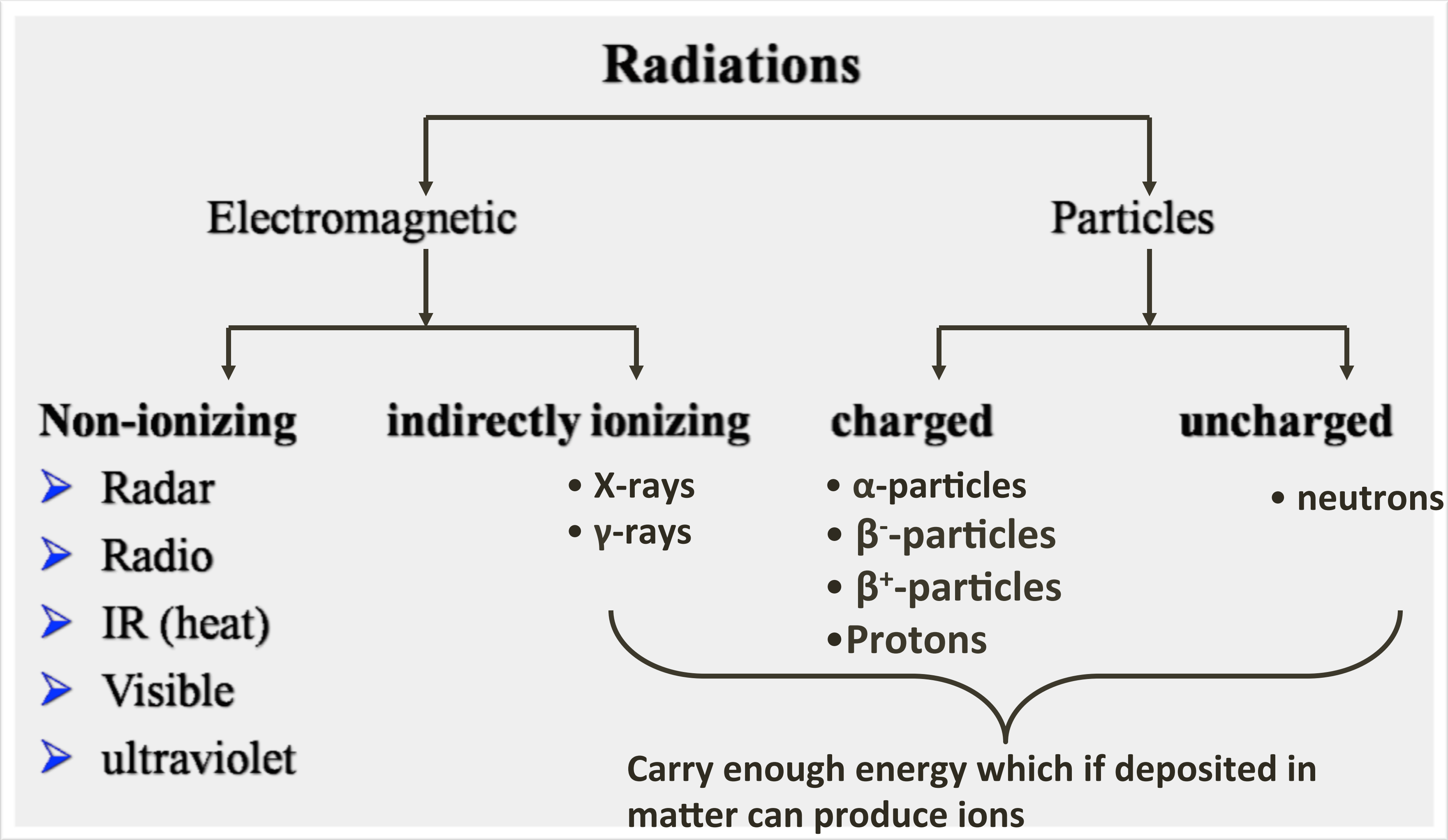
Possible cancer treatments:

- Surgery
- Chemiotherapy
- Radiotherapy:
  - Photons (X-Rays, gammas, …) → the most used
  - **Hadron therapy** (Protons, heavy ions) → increasing
  - Neutron (Mostly Neutron Boron capture)
- Combined therapies

Hadron therapy is a form of external beam radiotherapy using beams of energetic protons, or positive ions produced by cyclotrons and synchrotrons

→ Different effects with respect photons

Types of Radiations



Radiations

Electromagnetic

Particles

Non-ionizing

- Radar
- Radio
- IR (heat)
- Visible
- ultraviolet

indirectly ionizing

- X-rays
- γ-rays

charged

- α-particles
- β^--particles
- β^+-particles
- Protons

uncharged

- neutrons

Carry enough energy which if deposited in matter can produce ions

History of Hadron Therapy
A Time Line of Hadron Therapy

1938 Neutron therapy by John Lawrence and R.S. Stone (Berkeley)
1946 Robert Wilson suggests protons
1948 Extensive studies at Berkeley confirm Wilson
1954 Protons used on patients in Berkeley
1957 Uppsala duplicates Berkeley results on patients
1961 First treatment at Harvard (By the time the facility closed in 2002, 9,111patients had been treated.)
1968 Dubna proton facility opens
1969 Moscow proton facility opens
1972 Neutron therapy initiated at MD Anderson (Soon 6 places in USA.)
1974 Patient treated with pi meson beam at Los Alamos (Terminated in 1981) (Starts and stops also at PSI and TRIUMF)

History of Hadron Therapy (Cont)
A Time Line of Hadron Therapy

1975 St. Petersburg proton therapy facility opens
1975 Harvard team pioneers eye cancer treatment with protons
1976 Neutron therapy initiated at Fermilab. (By the time the facility closed in 2003, 3,100 patients had been treated)
1977 Bevalac starts ion treatment of patients. (By the time the facility closed in 1992, 223 patients had been treated.)
1979 Chiba opens with proton therapy
1988 Proton therapy approved by FDA
1989 Proton therapy at Clatterbridge
1990 Medicare covers proton therapy and Particle Therapy Cooperative Group (PTCOG) is formed:

1990 First hospital-based facility at Loma Linda (California)
1991 Protons at Nice and Orsay

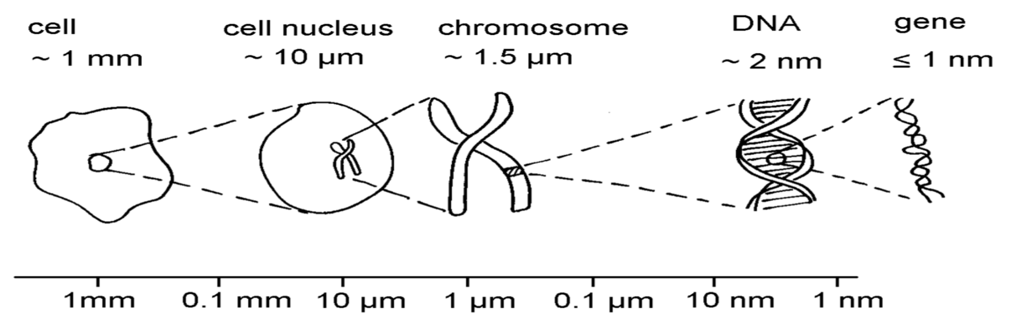
History of Hadron Therapy (Cont) A Time Line of Hadron Therapy

1992 Berkeley cyclotron closed after treating more than
2,500 patients
1993 Protons at Cape Town
1993 Indiana treats first patient with protons
1994 Ion (carbon) therapy started at HIMAC (By 20088
more than 3,000patients treated.)
1996 PSI proton facility
1998 Berlin proton facility
2001 Massachusetts General opens proton therapy center
2006 MD Anderson opens
2007 Jacksonville, Florida opens
2008 Neutron therapy re-stated at Fermilab (due to an ear mark).

Radiotherapy

Biological Effects

Radiation therapy idea



Selective cell destruction (cancer)

How it can be done?

By destroying the cell using Energy

Two diferent effects:

- Radiation damage a cell by altering it's atom

  Cause the atom's electron to become excited and then ionized

  → Free radicals (hydroxil) for water → Oxygen needed

  Enzymes try repair this damage, but in cancer cell it happens slower than in healthy cell → cancer cell end up dying more than healthy cell

- Radiation (hadrons) damage directly DNA (double strand breaks) → almost impossible to repair → effective on all molecules

Reminder

- Absorbed dose D is the energy (joules) deposited per unit mass (kg) of target material, D = dE/dm.
- The special unit of absorbed dose D is the Gray (Gy) ≡ 1 Joule/kg
- In biological systems
- Radiation → Biologic effects → dependent on "the spatial distribution of energy deposition" (LET)

LET = Linear Energy Transfer is energy deposited per unit path length = dE/dx with units ev/cm

Radiotherapy: the goal

In order to treat cancer :

The main goal is to delivers a defined dose distribution within the target volume (CANCER) and none outside it.

What type of radiation would be the Best??

Treatment options

1) **Photon therapy.**

2) Proton therapy.

3) Heavy-ion (Carbon) therapy.

Interactions of Photons

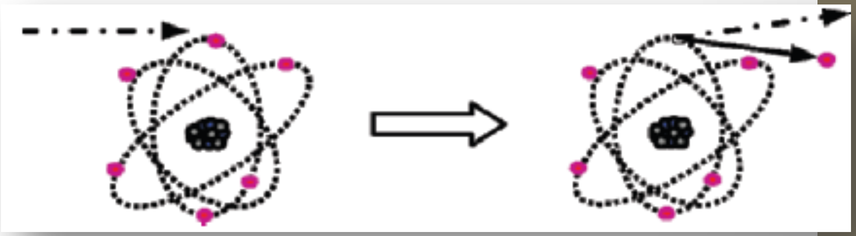
Three interaction modes:

- Photo-electric effect.

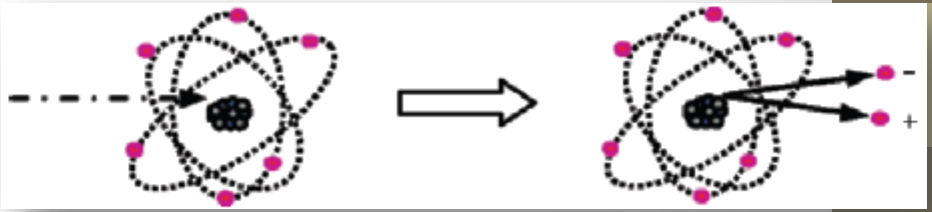
Entire energy transfer from photon to an atomic electron .

- Compton effect.

Fraction of energy transferred to Compton electrons.



- Pair production.

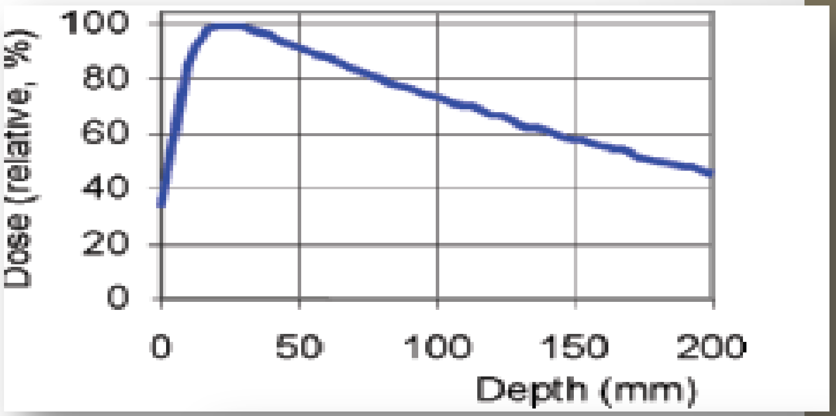


What happen when a beam of photon entering a tissue ?

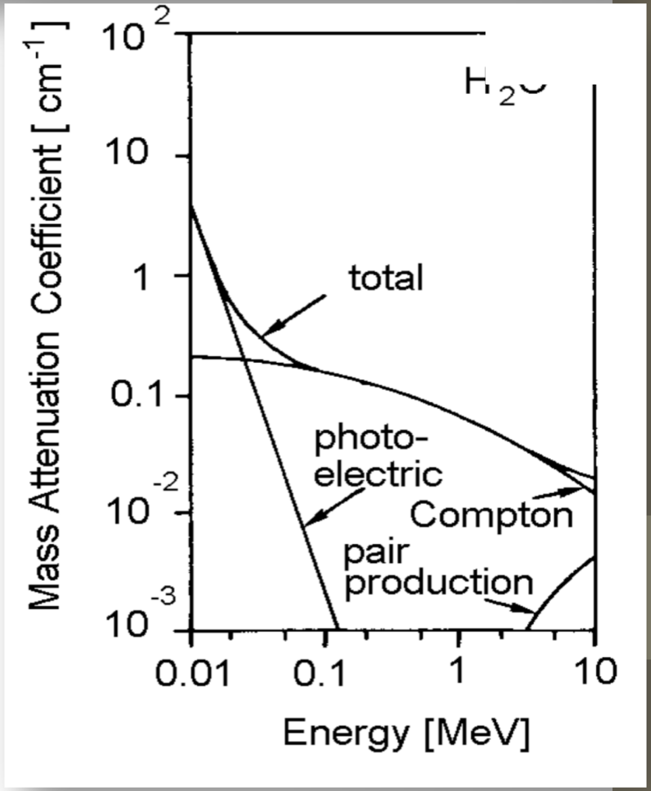
Exponential behaviour

- It falls exponentially

$$E = E_o \exp(-\mu_{en} x)$$



- Number of photon gets attenuated as depth increases .
- As their number decreases, the dose that they deposit decreases also (proportionately).



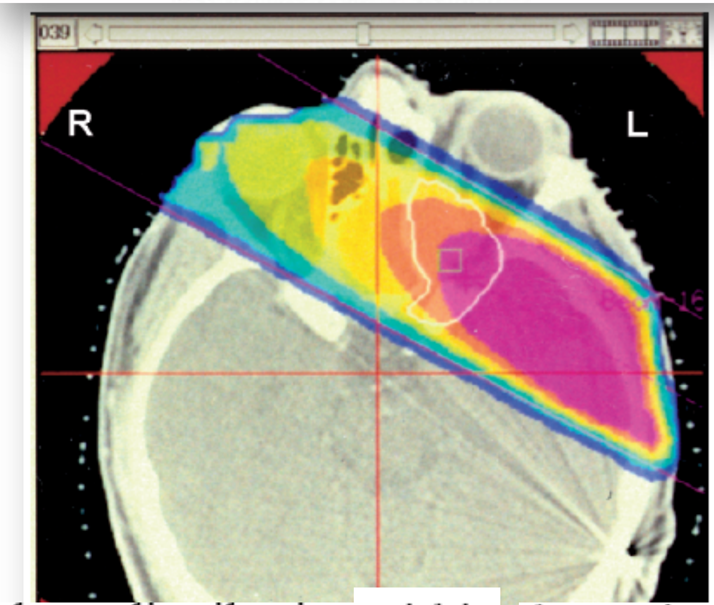
Photon’s therapy drawbacks

Based on “how radiation interacts with matter”

The drawbacks:

- Most of the radiation is deposited on healthy tissue.
- Not easy to control where the energy is deposited (low mass & high energy)
- Low **LET**

Click image to enlarge.



dose distribution within the patient

>30 >50 >70 >80 >90 >98

Treatment options

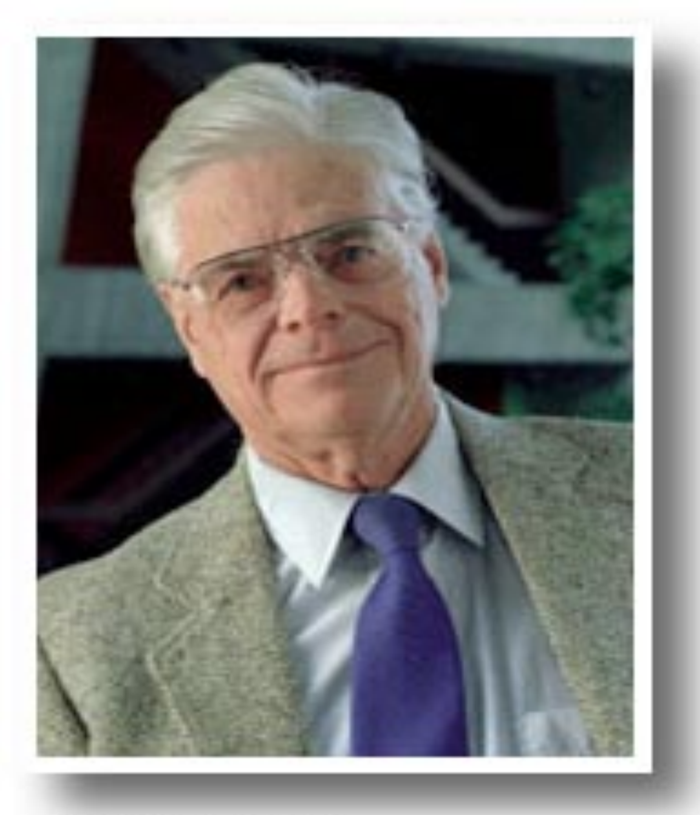
1) Photon therapy.

2) **Proton therapy.**

3) Heavy-ion (Carbon) therapy.

The original idea

- In 1946 Harvard physicist Robert Wilson (1914-2000) suggested*:
  - **Protons can be used clinically**
  - **Accelerators are available**
  - **Maximum radiation dose can be placed into the tumor**
  - **Proton therapy provides sparing of normal tissues**
  - **Modulator wheels can spread narrow Bragg peak**



Robert Wilson

*Wilson, R.R. (1946), “Radiological use of fast protons,” Radiology 47, 487.

Physical basis of Hadron Therapy

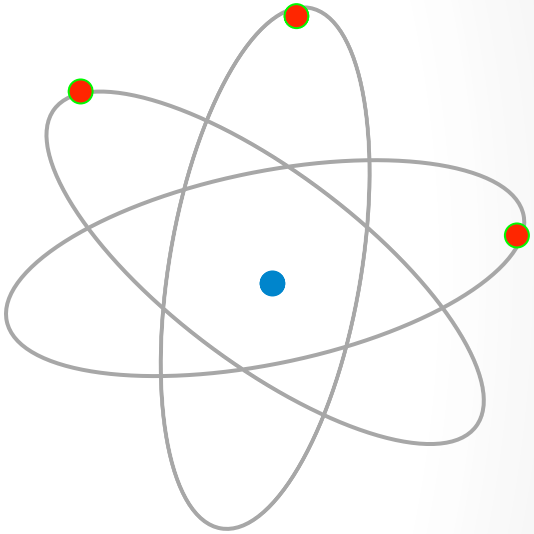
- In Hadron therapy energetic ionizing particles (protons or carbon ions) are directed at the target tumor.
- The dose increases while the particle penetrates the tissue, up to a maximum (the Bragg peak) that occurs near the end of the particle's range, and it then drops to (almost) zero.
- The advantage of this energy deposition profile is that less energy is deposited into the healthy tissue surrounding the target tissue.

Moreover more precise positioning of the energy deposition

Characteristics of protons

- Subatomic particle .
- Stable , positively charged .
- Heavy particle with mass 1800 that of electron.
- Very little scattered as they travel through tissue .
- Travel in straight lines.

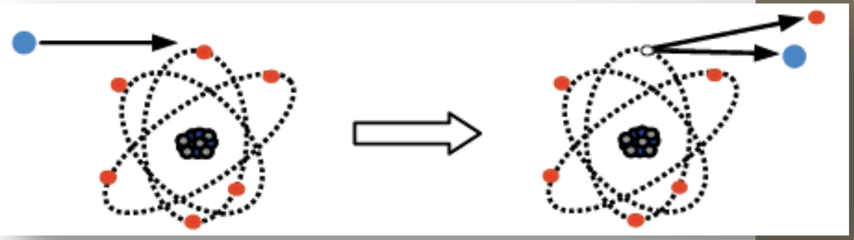
→ Very different modes of interactions with matter .



Interactions of Protons

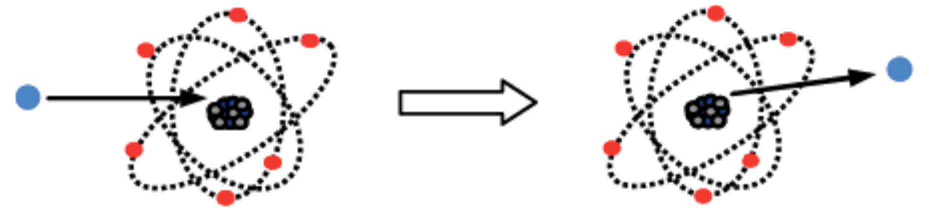
- Coulomb interactions with atomic electrons .

Electronic (ionization ,excitation)



- Coulomb interactions with atomic nuclei .

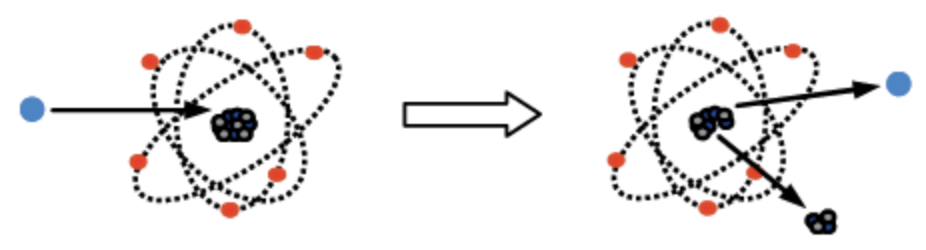
“multiple Coulomb scattering.”



- Nuclear interactions with atomic nuclei .

Elastic nuclear collisions

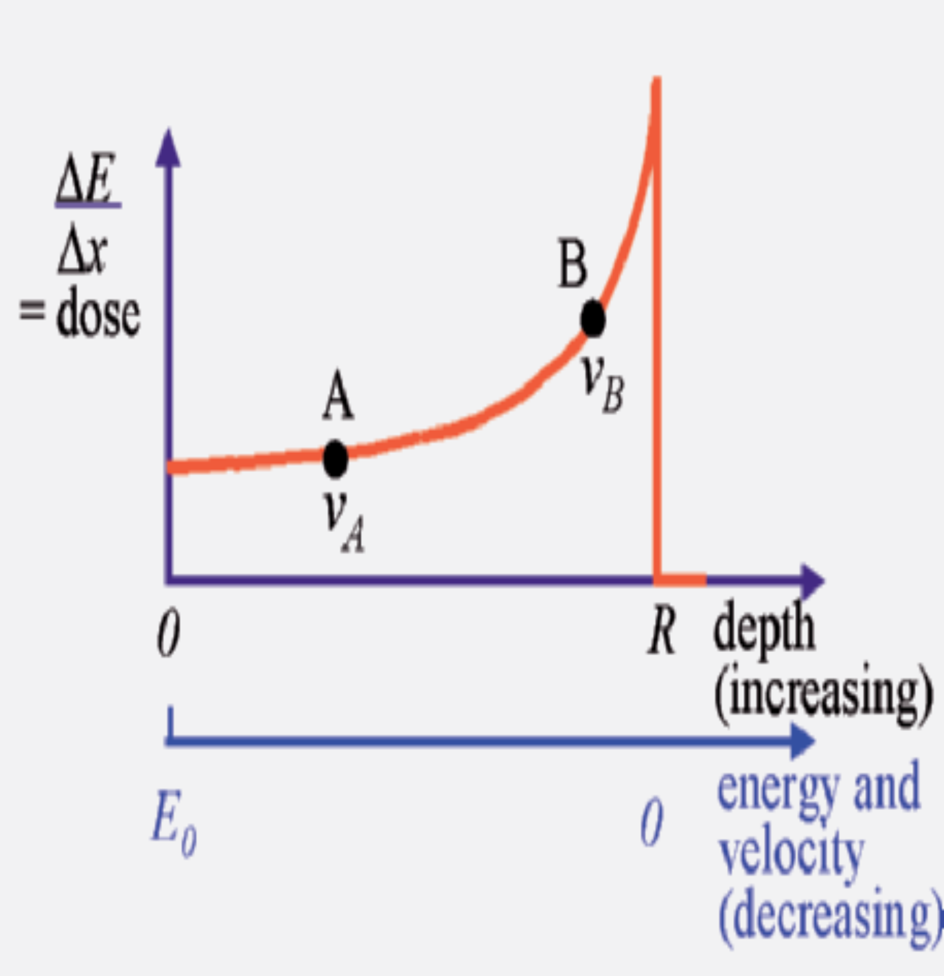
Non elastic nuclear collisions



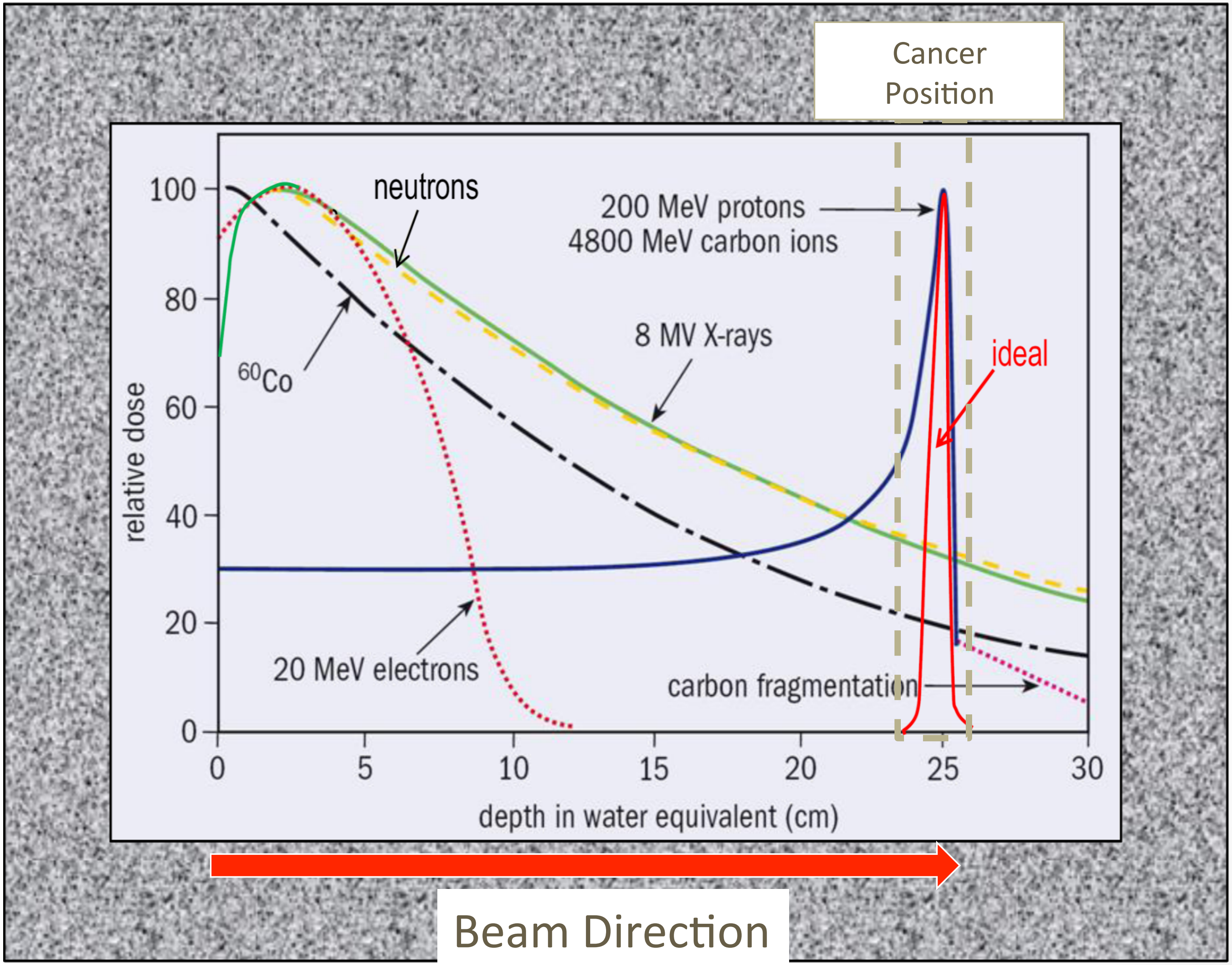
The "Bragg peak"

- Protons are loosing less energy when entering tissue, depositing more and more as they slow down and a huge dose of radiation just before they stop, giving rise to the so-called Bragg peak
- The proton "linear energy transfer" (LET) is given by the Bethe-Block formula:

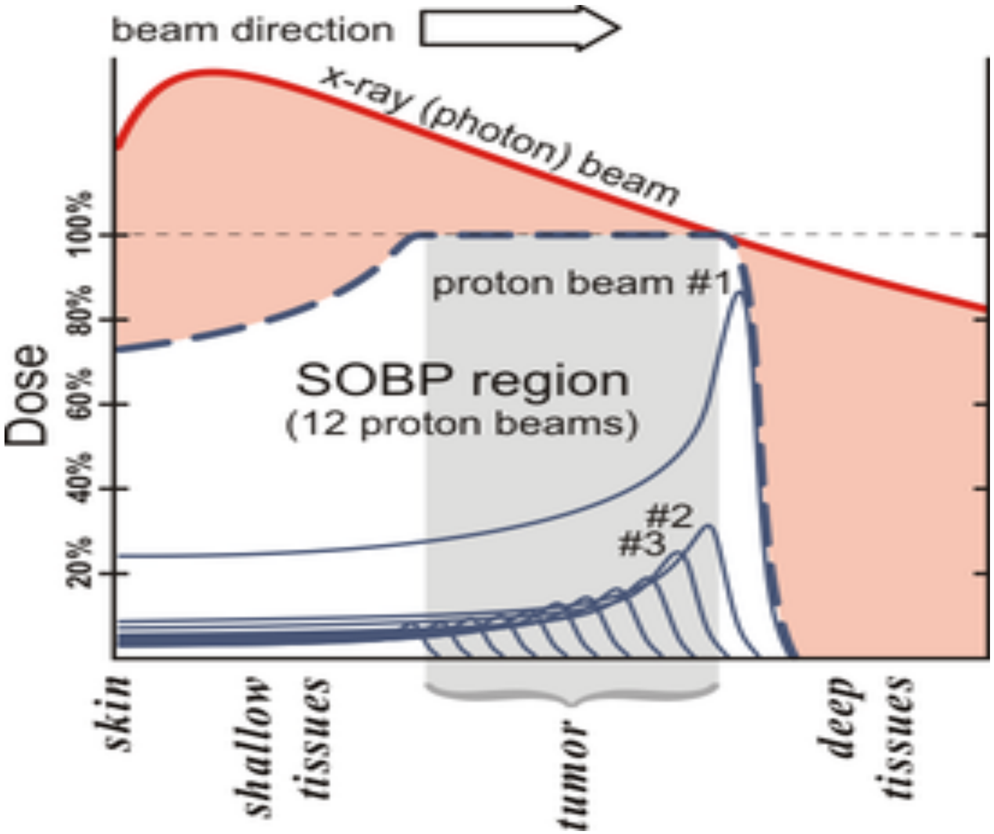
$$\frac{dE}{dx} \propto \frac{1}{v^2}\left(\frac{Z}{A}\right)z^2$$

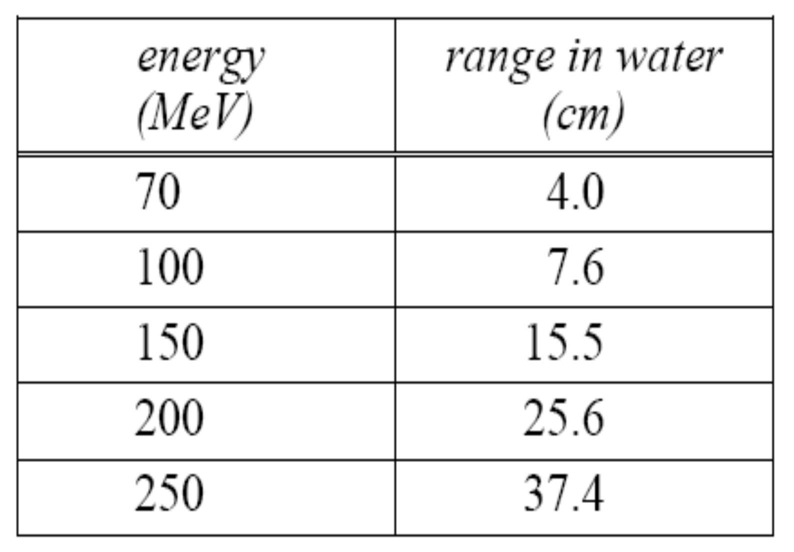


Energy deposition vs particle type



The spread-out Bragg peak (SOBP)



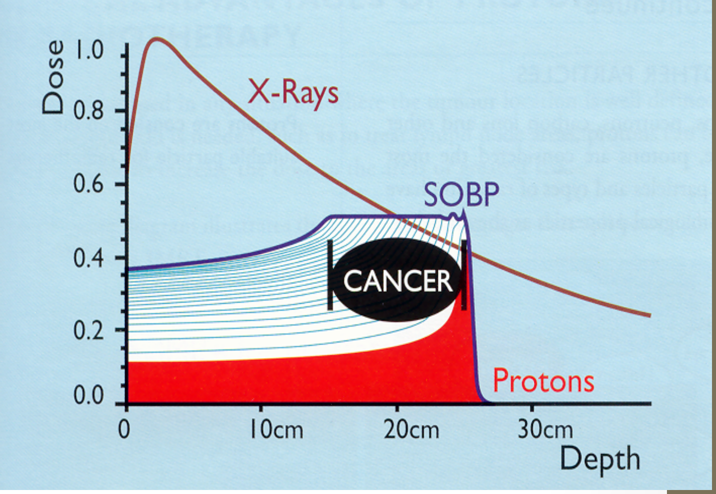


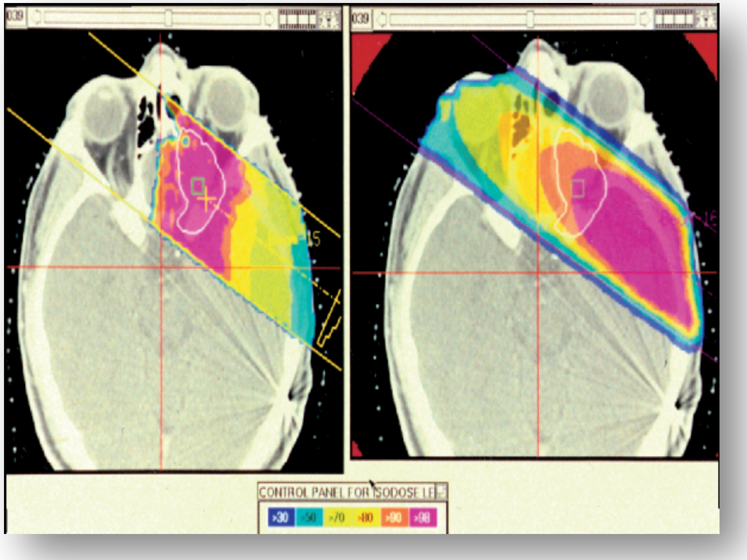
energy (MeV)	*range in water (cm)*
70	4.0
100	7.6
150	15.5
200	25.6
250	37.4

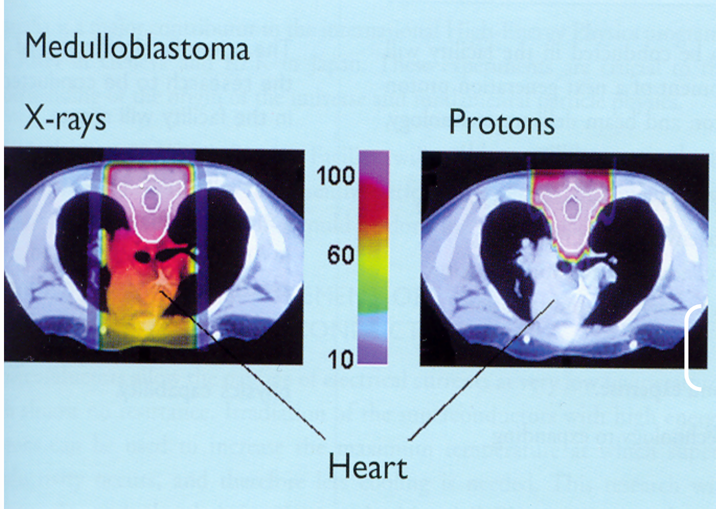
In most treatments, protons of different energies with Bragg peaks at different depths are applied to treat the entire tumor

Why Protons are advantageous

- Relatively low entrance dose (plateau)
- Maximum dose at depth (Bragg peak)
- Rapid distal dose fall-off
- Energy modulation (Spread-out Bragg peak)







proton therapy may be used to treat these cancers:

- Central nervous system cancers (including chordoma, chondrosarcoma, and malignant meningioma)
- Eye cancer (including uveal melanoma or choroidal melanoma)
- Head and neck cancers (including nasal cavity and paranasal sinus cancer and some nasopharyngeal cancers)
- Lung cancer
- Liver cancer
- Prostate cancer
- Spinal and pelvic sarcomas (cancers that occur in the soft-tissue and bone)
- Some noncancerous tumors of the brain may also benefit from proton therapy.

Application

- Proton therapy goes to a specific area of the patient's body, so this therapy can best shrink tumors that have not spread to other parts of the body
- proton therapy alone, or they may combine with standard radiation therapy, surgery, and/or chemotherapy are used clinically .
- Proton therapy is particularly useful for treating cancer in children because it lessens the chance of harming healthy, developing tissue.

Treatment options

1) Photon therapy.

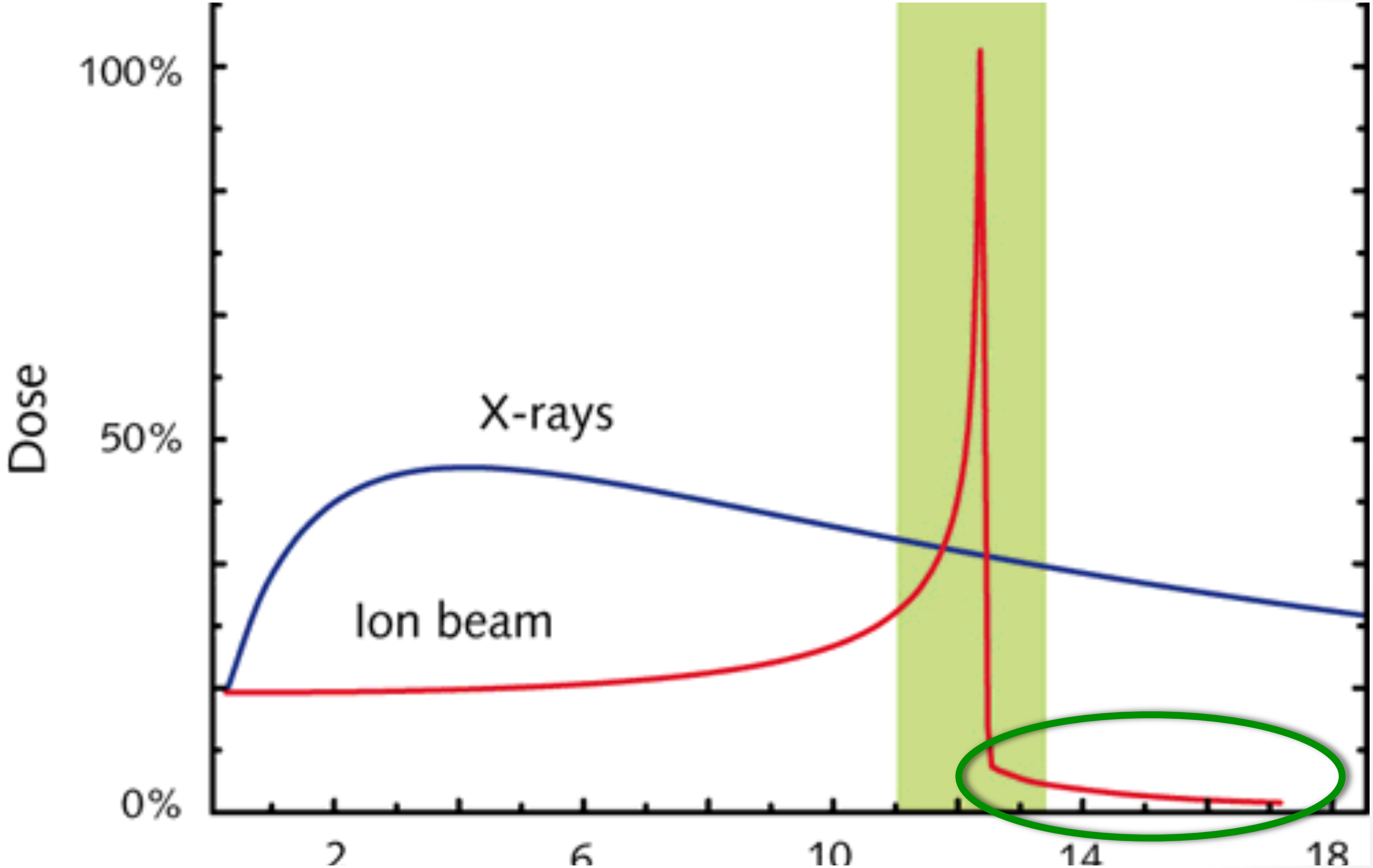
2) Proton therapy.

3) **Heavy-ion (Carbon) therapy.**

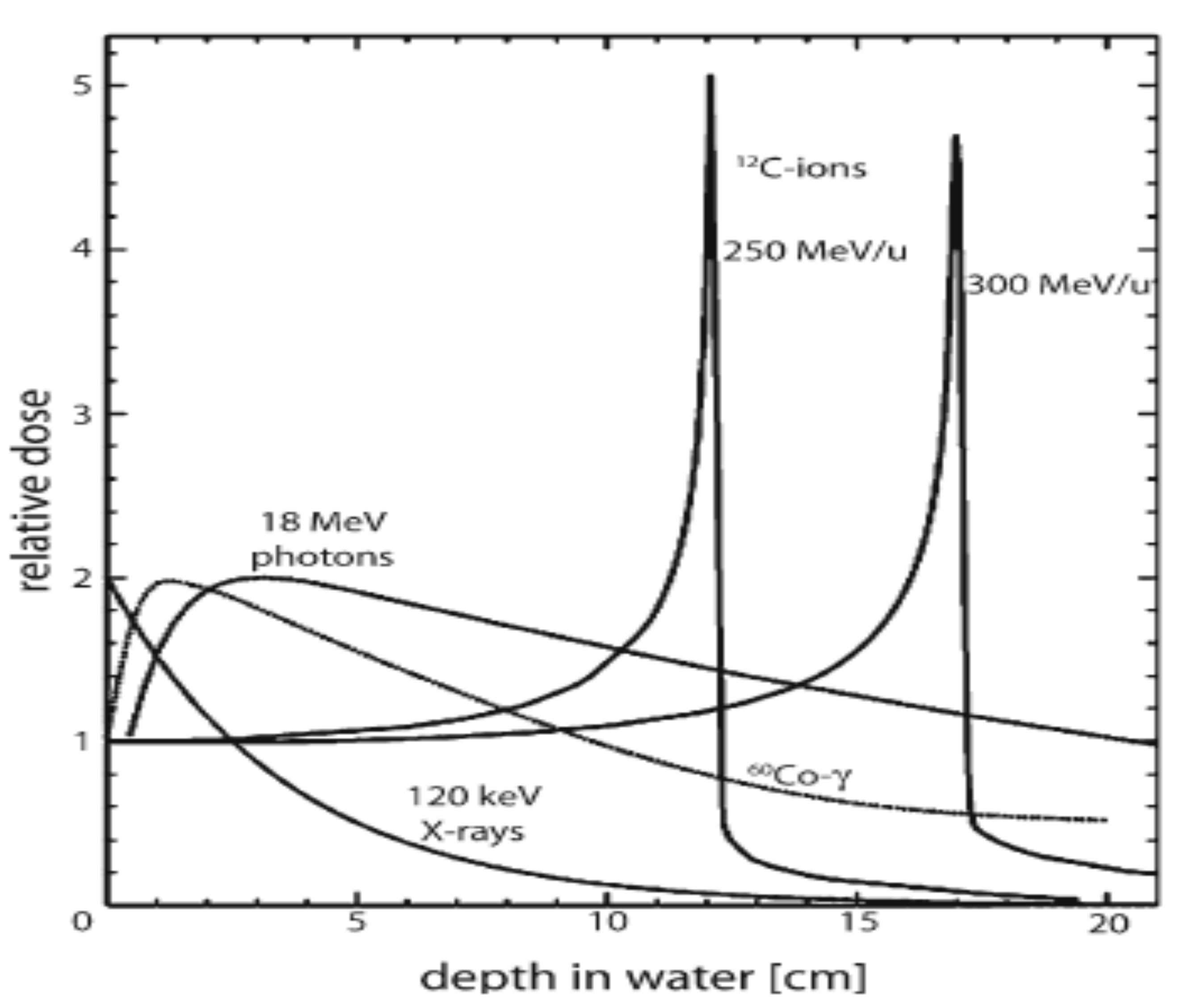
Heavy ion therapy

- Heavy-ion therapy is the use of particles more massive than protons or neutrons, such as carbon ions
- They are produced in ion sources and accelerated up to 50% of the speed of light in order to reach the necessary depth in the patient.
- A typical therapy beam consists of 1 million to 10 million carbon ions per second .

Physical basis of heavy ion therapy



Different beam energies



Advantages

As compared to conventional radiotherapy, heavy ion radiotherapy has the following advantages:

- Higher tumor dose and improved sparing of normal tissue in the entrance channel
- More precise concentration of the dose in the target volume with steeper gradients to the normal tissue
- Higher radiobiological effectiveness for tumors which are radio-resistant during conventional
- Oxygen effect heavy-ion irradiation overcomes the effect of tumor hypoxia
- The high LET heavy-ion irradiation causes many ionizations as they traverse a cell, and double-strand breaks of the DNA molecule are possible. DNA repair of double-strand breaks are much more difficult for a cell to repair, and more likely to lead to cell death.

Application carbon ion therapy

In general radio-resistant cancers as:

- Prostate cancer
- Lung cancer
- Specific bone and soft-tissue sarcomas
- Pancreas (under study)

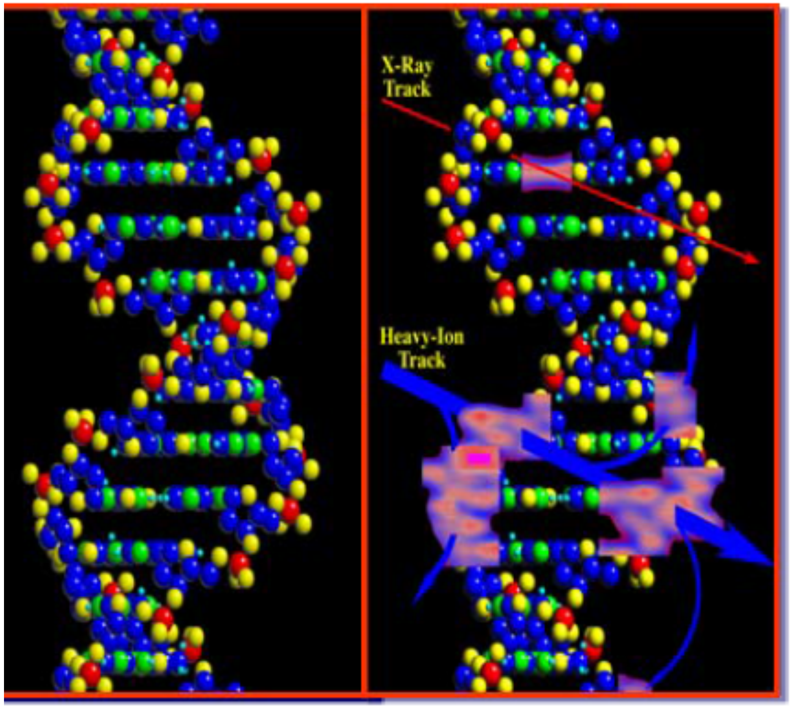
Disadvantage wrt protons

Compared to protons, carbon ions have the disadvantage that beyond the Bragg peak, the dose does not decrease to zero, since nuclear reactions between the carbon ions and the atoms of the tissue lead to production of lighter ions which have a higher range. Therefore, some damage occurs also beyond the Bragg peak.

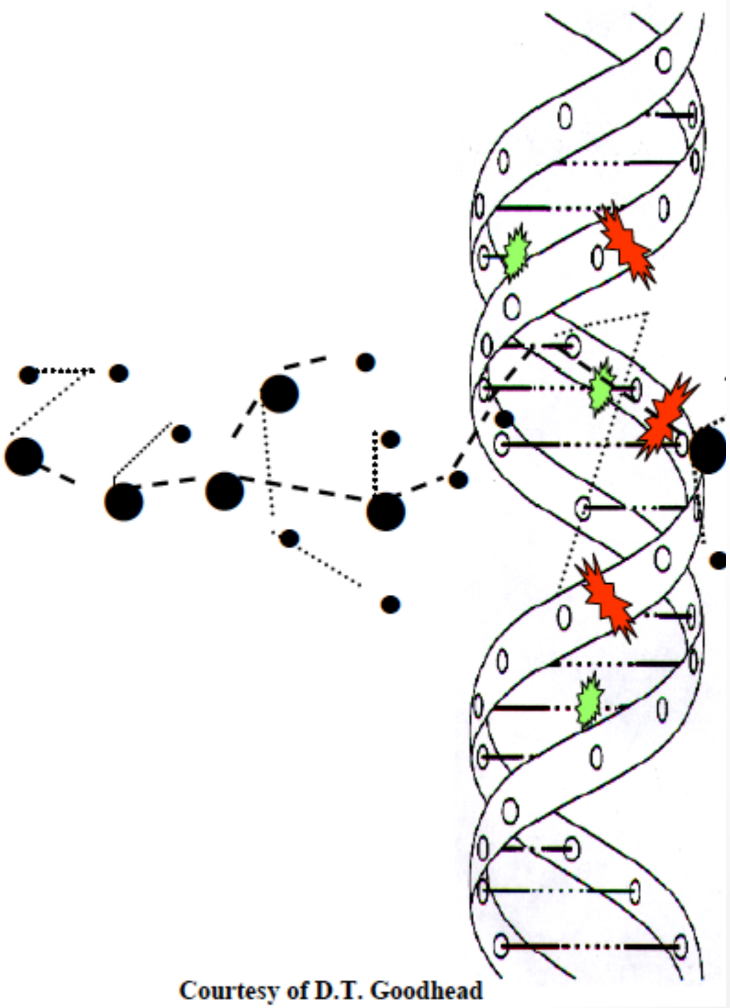
WHY ?

The most unkindest cut at all

(W. Shakespeare, Julius Caesar, Act. 3)



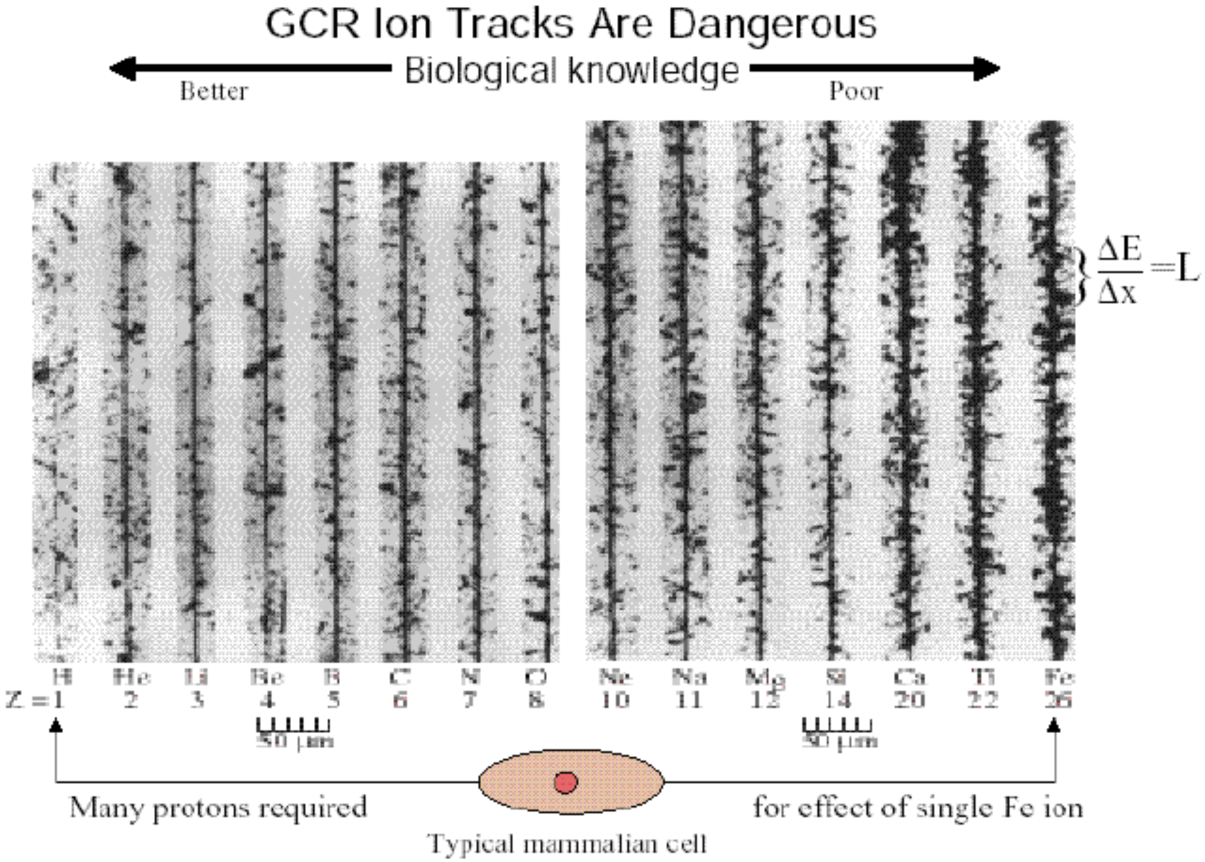
Courtesy of NASA

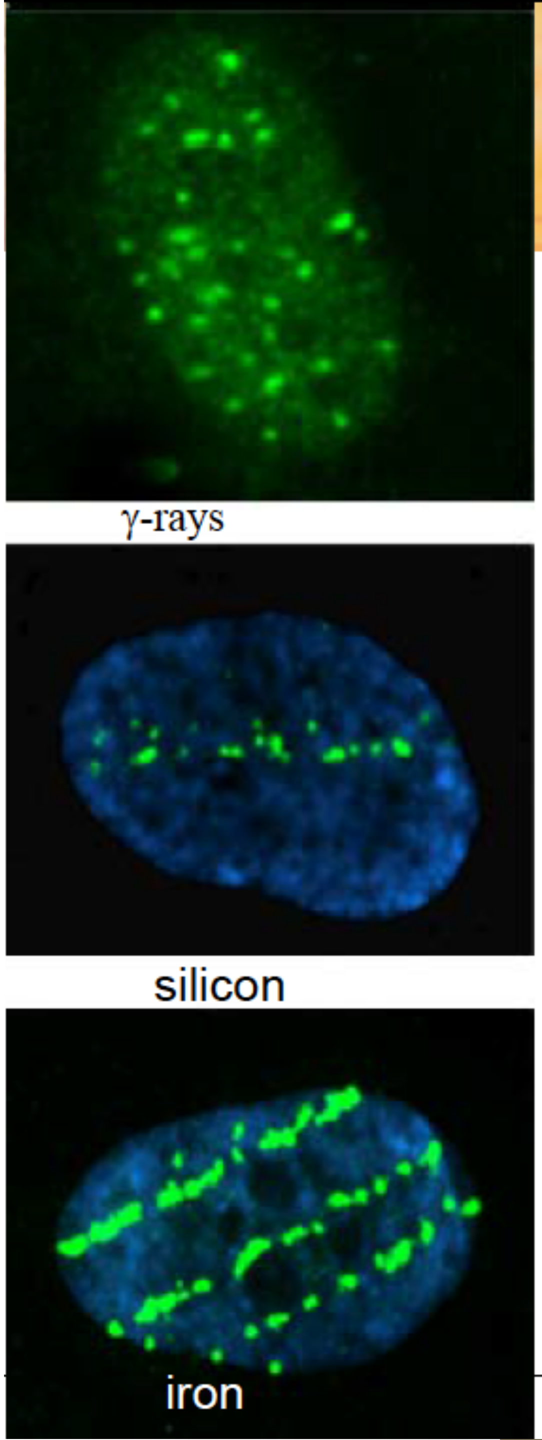


Courtesy of D.T. Goodhead

Double strain break

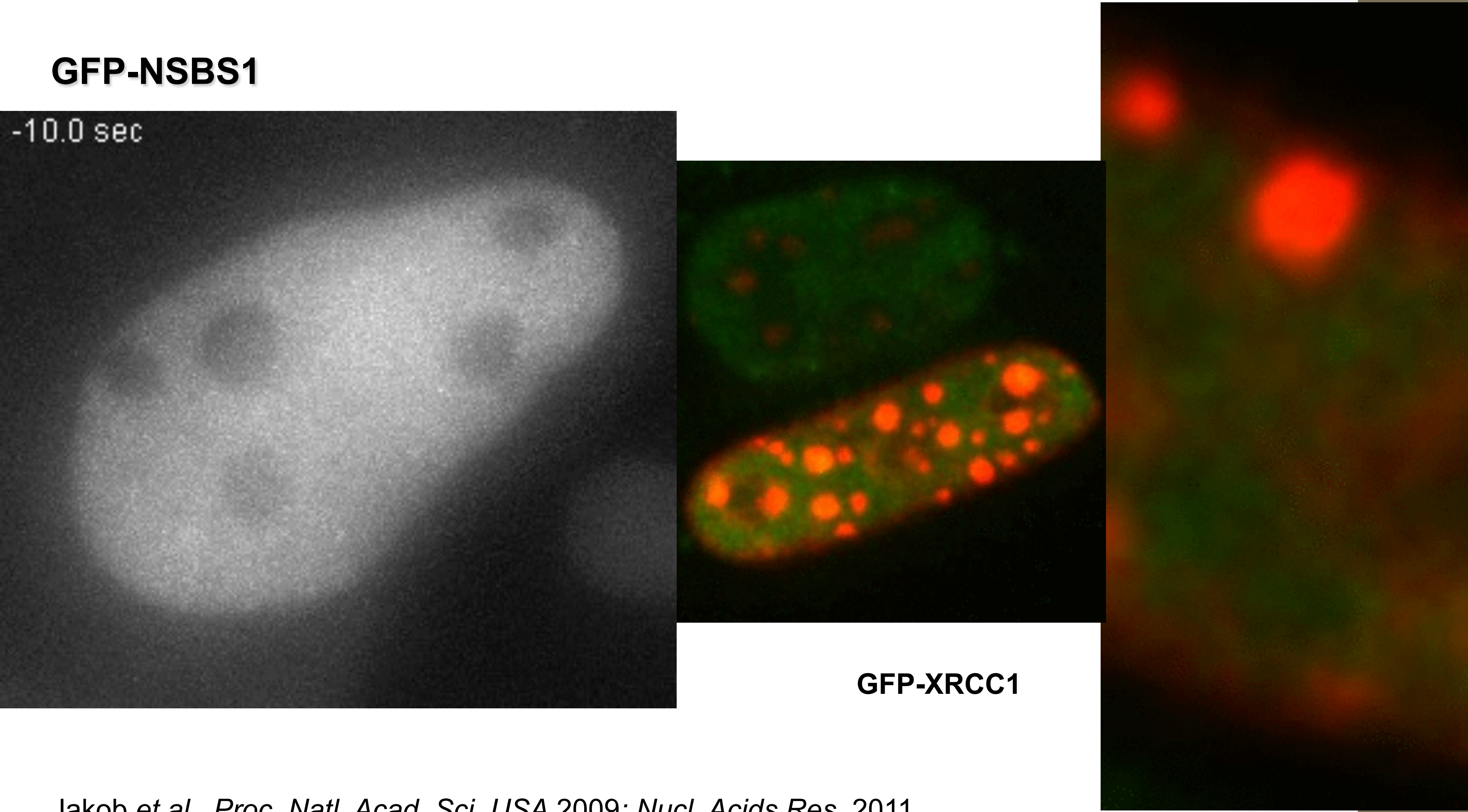
Track in cells





Live cell imaging of heavy ion traversals in euchromatin and heterochromatin

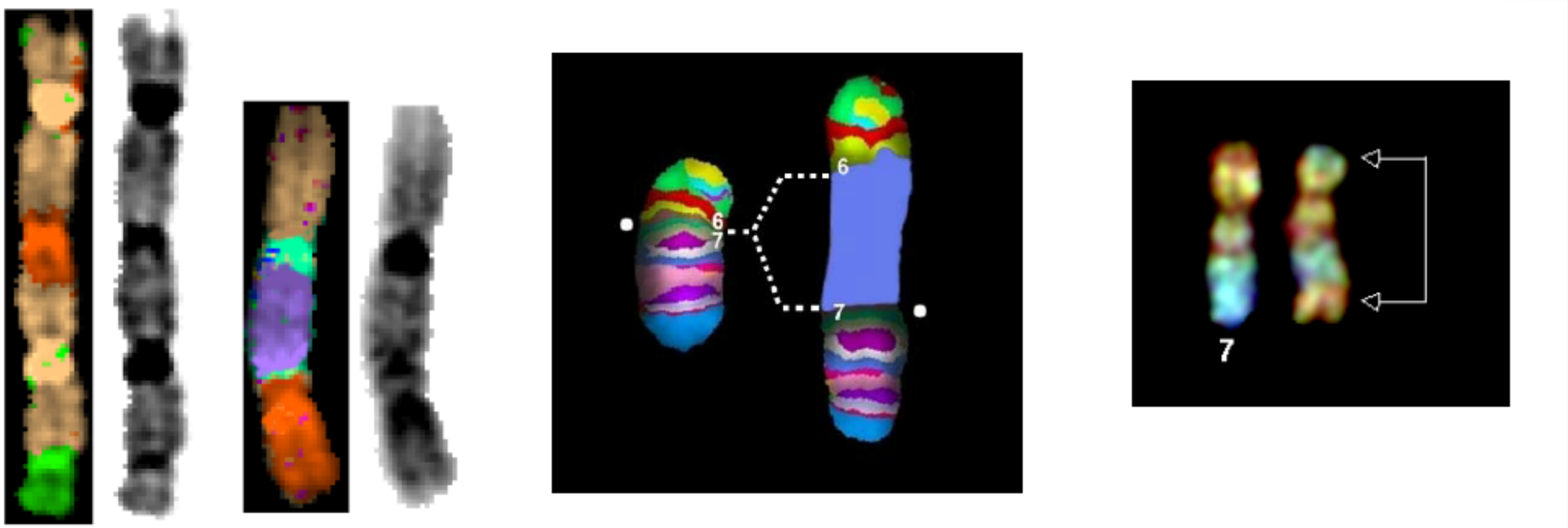
GFP-NSBS1

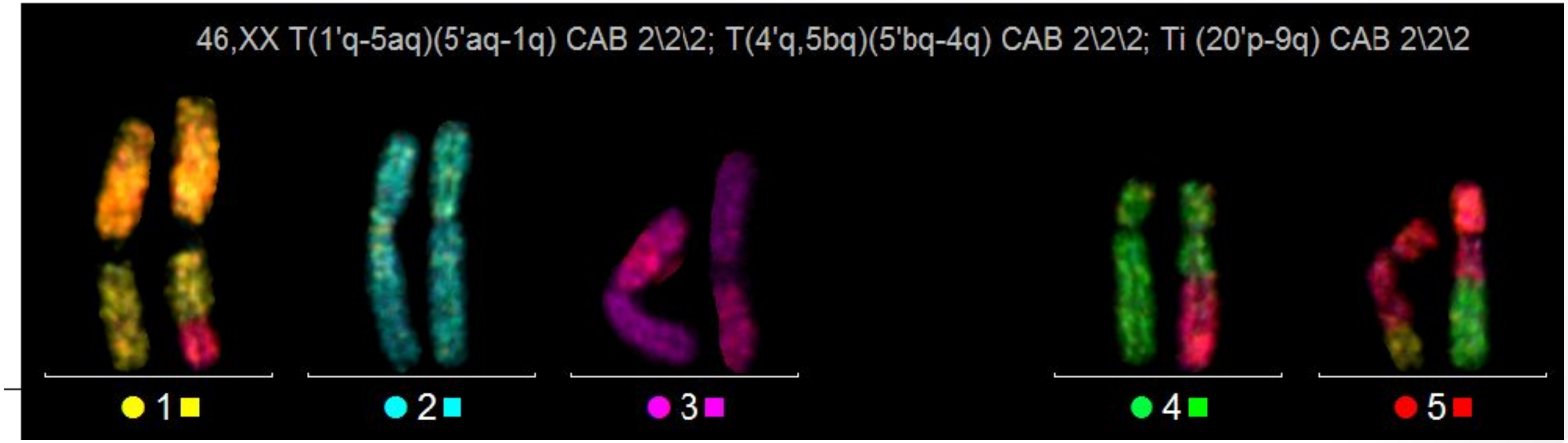


GFP-XRCC1

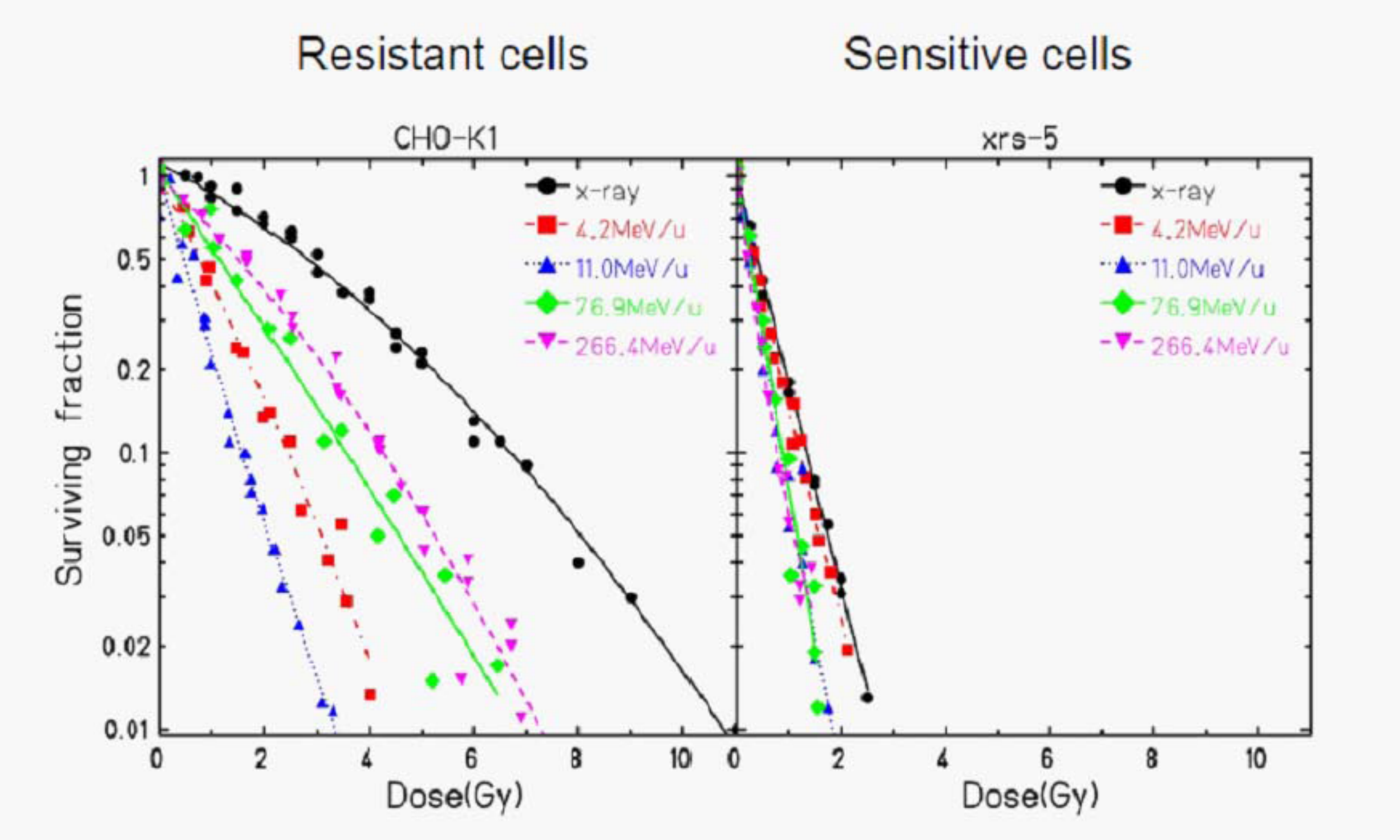
Jakob *et al., Proc. Natl. Acad. Sci. USA* 2009; *Nucl. Acids Res*. 2011

Fro DNA to chromosomes
Heavy ion induced rearrangement

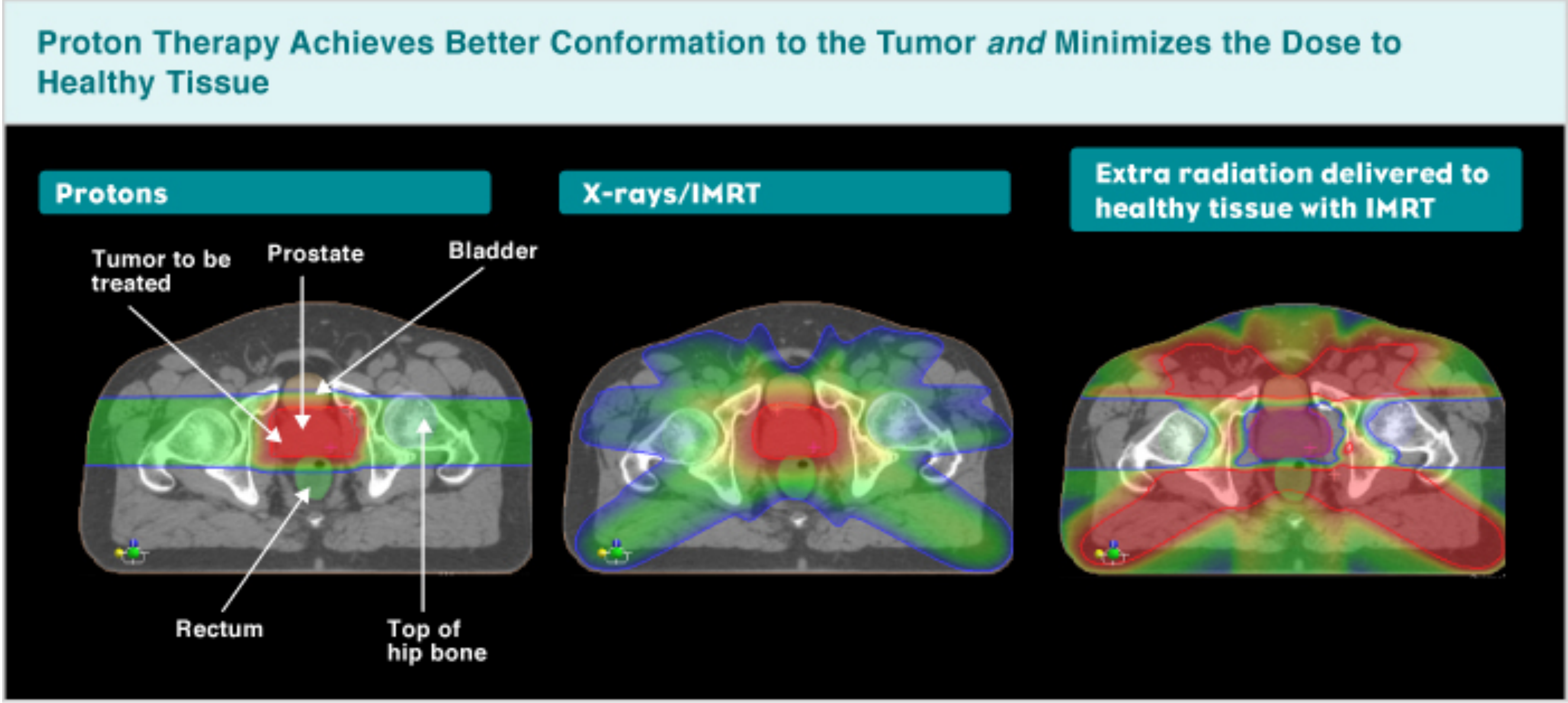



46,XX T(1'q-5aq)(5'aq-1q) CAB 2\2\2; T(4'q,5bq)(5'bq-4q) CAB 2\2\2; Ti (20'p-9q) CAB 2\2\2

……. to cell killing ….



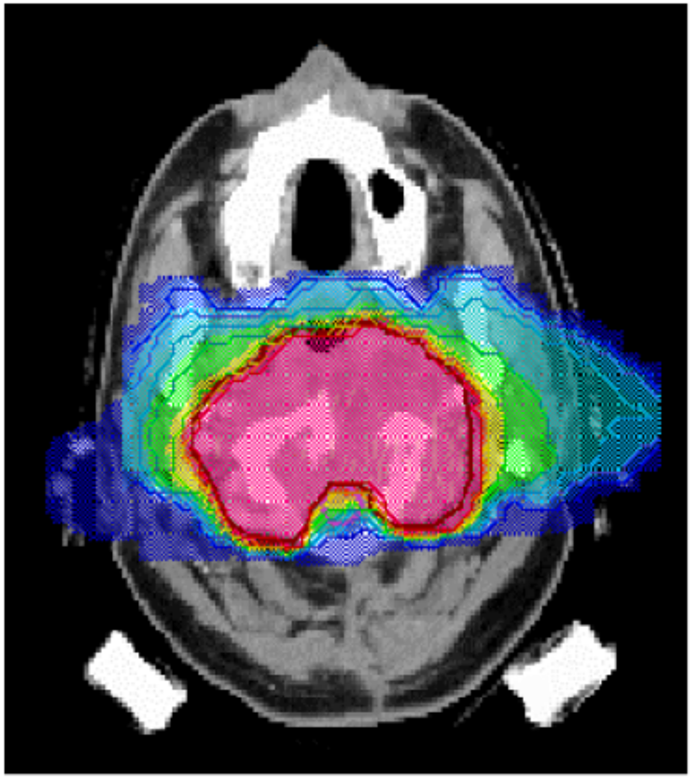
Treatment plans with protons: prostate



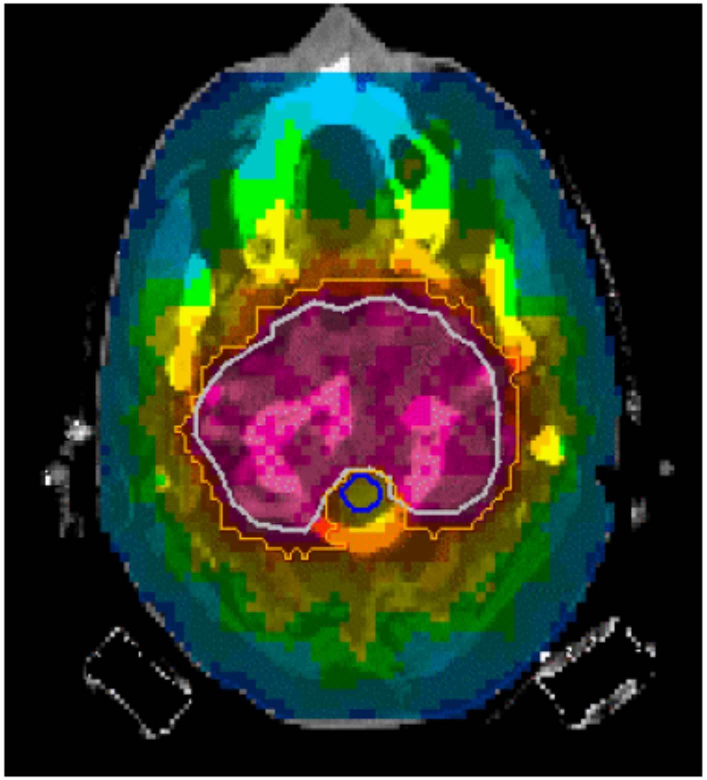
Proton Therapy Achieves Better Conformation to the Tumor *and* Minimizes the Dose to Healthy Tissue

Courtesy of Reinhold Schulte, LLUMC

Treatment of the base of the skull



C-ions, 2 fields



IMRT, 9 fields

Incidence of Second Malignancies Among Patients Treated With Proton Versus Photon Radiation

Christine S. Chung, MD, MPH,* Torunn I. Yock, MD, MCh,[†] Kerrie Nelson, PhD,[‡] Yang Xu, MS,[§] Nancy L. Keating, MD, MPH,[§,¶] and Nancy J. Tarbell, MD[†,||]

International Journal of Radiation Oncology
biology • physics

MGH
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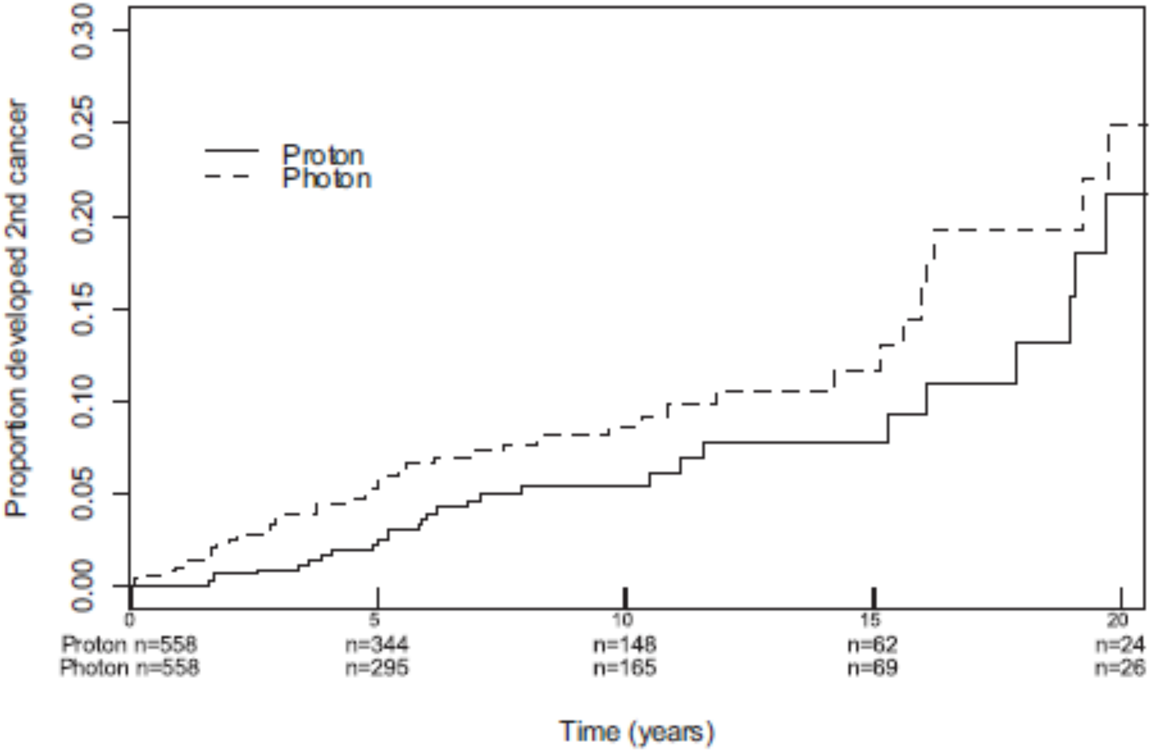


Nuclear physics: new solutions to set the controversy

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

BMJ VOLUME 327 20–27 DECEMBER 2003

Gordon C S Smith, Jill P Pell

Proton Therapy for Prostate Cancer

Although this is the most common use of proton therapy, controversy remains

BJC

British Journal of Cancer (2013) 108, 1225–1230 | doi: 10.1038/bjc.201

Keywords: proton beam; radiation; prostate cancer; quality of life; cost; evidence

Proton beam therapy and localised prostate cancer: current status and controversies

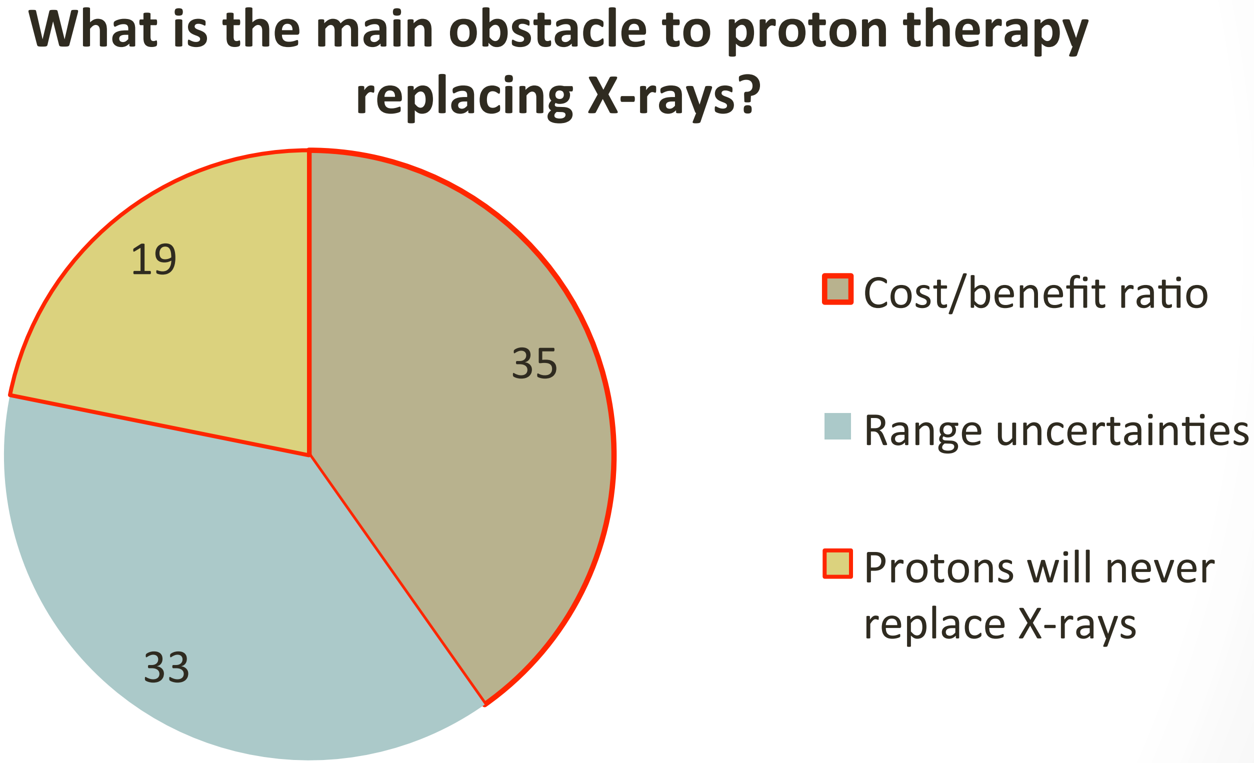
J A Efstathiou*[1], P J Gray[1] and A L Zietman[1]

[1]Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

Particle therapy “perceived as too expensive, too complicated, not enough precise and reliable” (from *Bloomberg Business*, 2012)

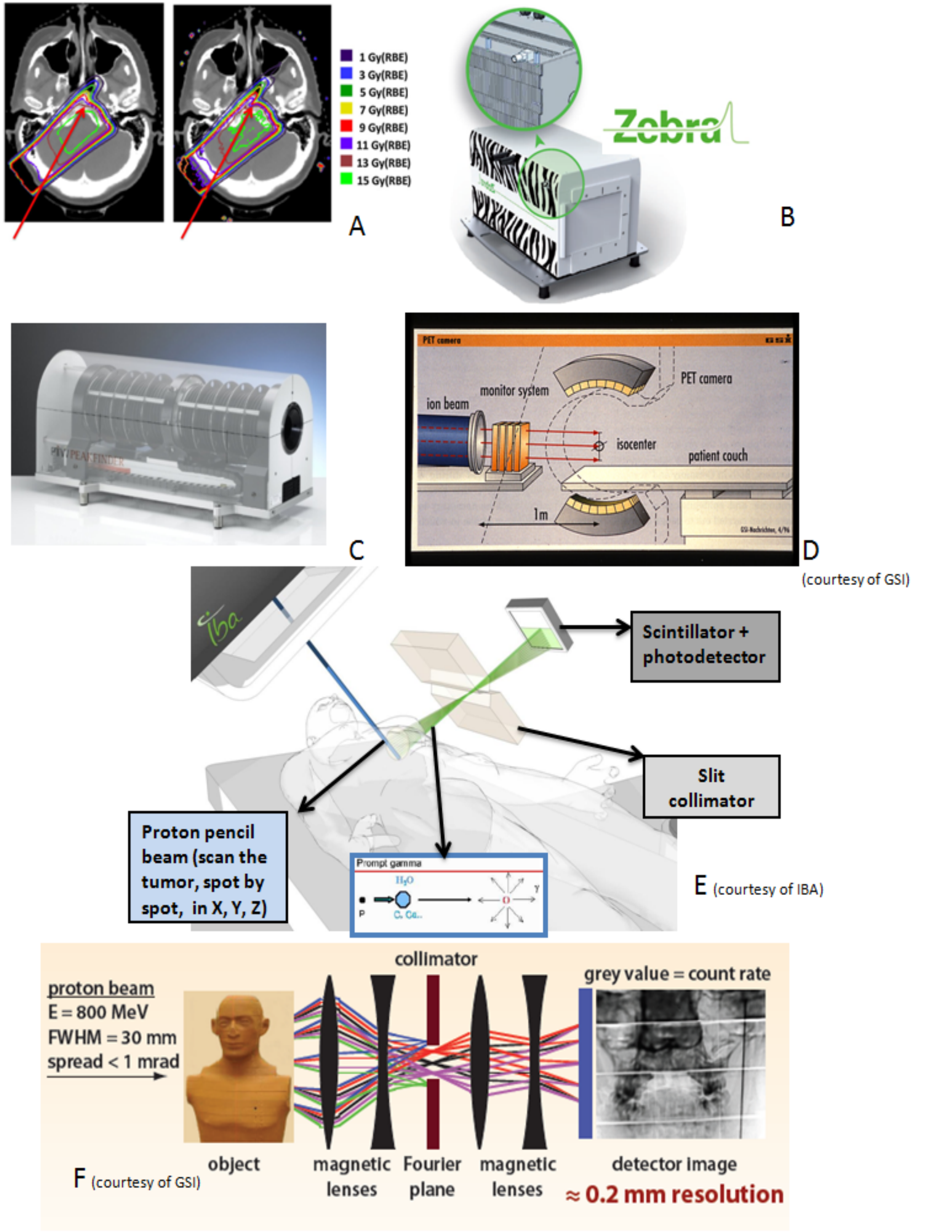
AAPM poll, August 2012


What is the main obstacle to proton therapy replacing X-rays?

Range uncertainty

Range verification

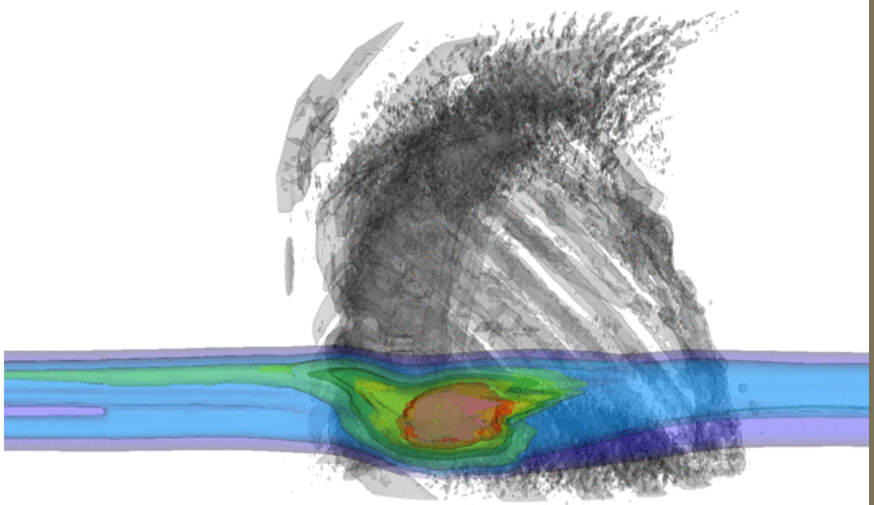
Source of range uncertainty in the patient	Range uncertainty
Independent of dose calculation:	
Measurement uncertainty in water for commissioning	± 0.3 mm
Compensator design	± 0.2 mm
Beam reproducibility	± 0.2 mm
Patient setup	± 0.7 mm
Dose calculation:	
Biology (always positive)	+ 0.8 %
CT imaging and calibration	± 0.5 %
CT conversion to tissue (excluding I-values)	± 0.5 %
CT grid size	± 0.3 %
Mean excitation energies (I-values) in tissue	± 1.5 %
Range degradation; complex inhomogeneities	- 0.7 %
Range degradation; local lateral inhomogeneities *	± 2.5 %
Total (excluding *)	**2.7% + 1.2 mm**
Total	**4.6% + 1.2 mm**

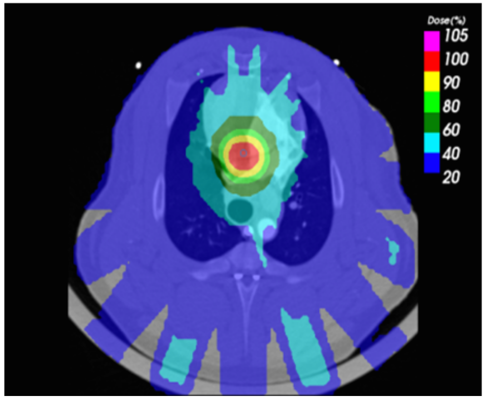


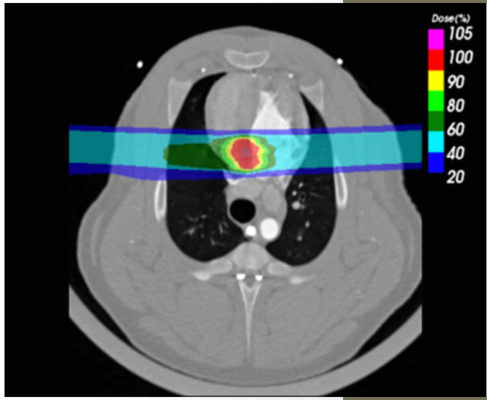
NuPECC report „Nuclear Physics in Medicine“, 2014

Improving benefit: new tumors and diseases

- **Established clinical indications**
  - Skull base and spine tumors
  - Hepatocellular carcinoma
  - Eye tumors
  - Pediatric tumors
- **More research needed for**
  - Thoracic malignancies
  - Head and Neck tumors
  - Pelvic and abdominal sites
  - Metastatic disease
  - Noncancer diseases





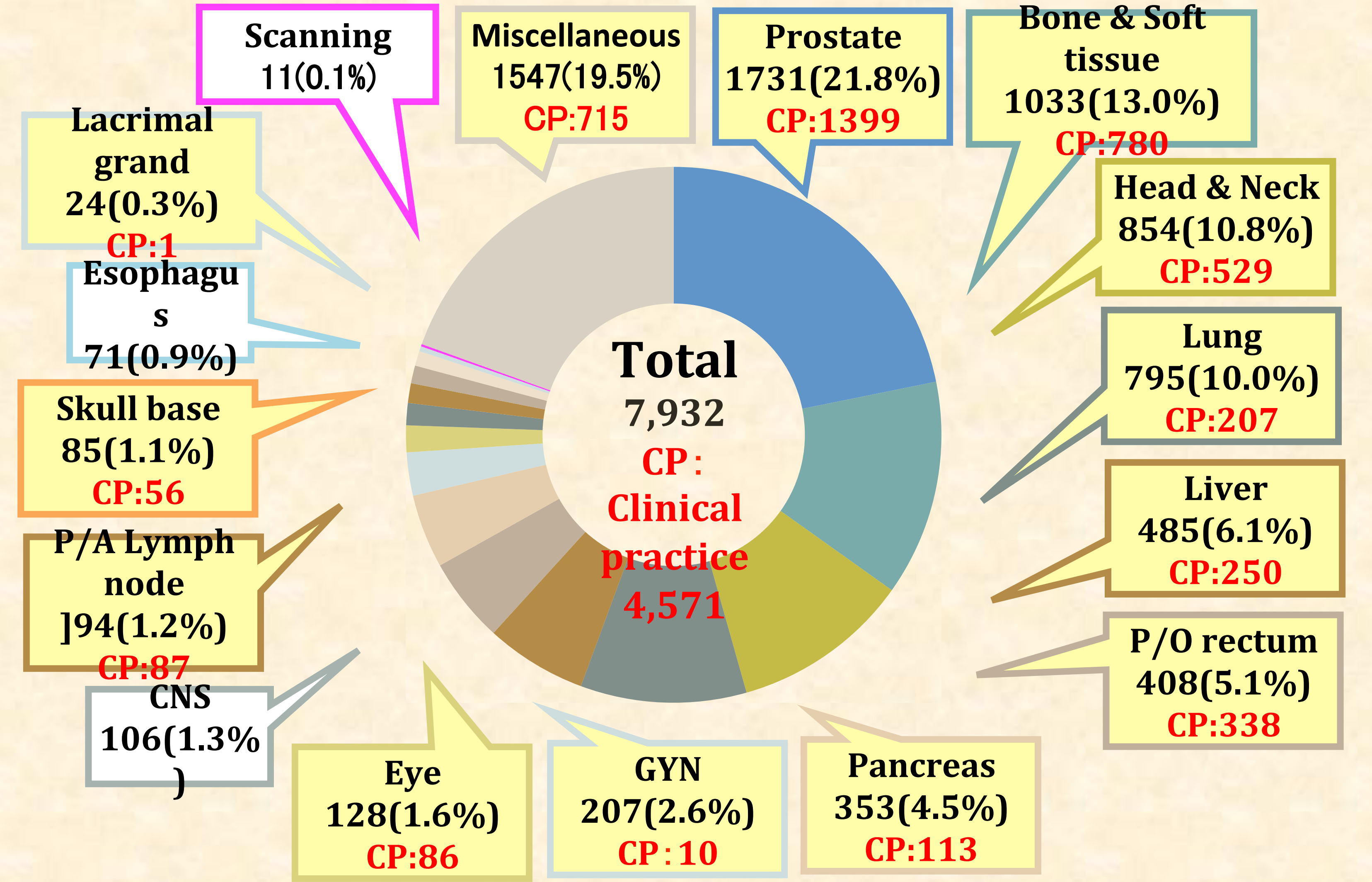


ASTRO Model Policy, May 2014

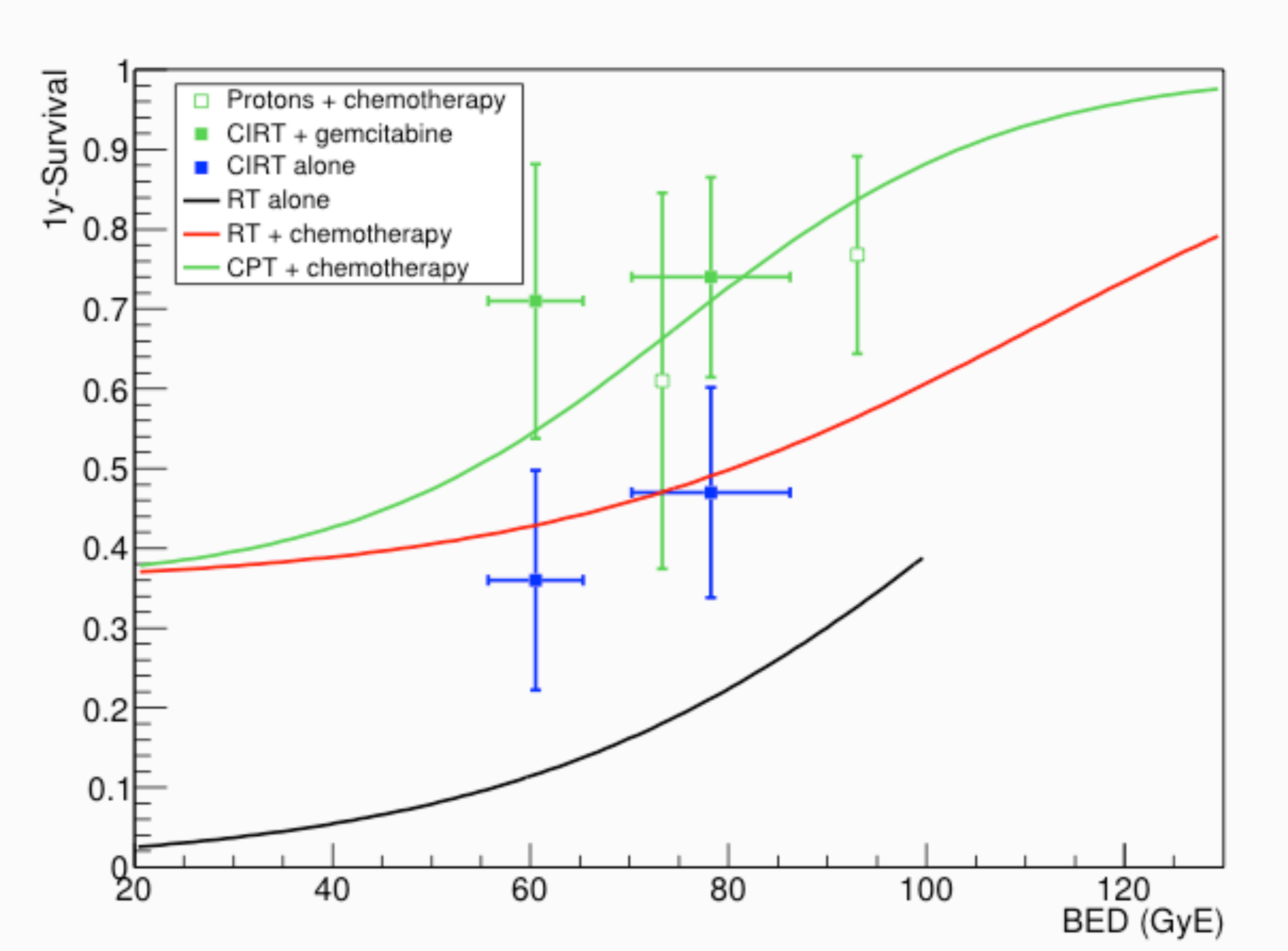
Carbon ion radiotherapy in Japan: an assessment of 20 years of clinical experience

www.thelancet.com/oncology Vol 16 February 2015

Tadashi Kamada, Hirohiko Tsujii, Eleanor A Blakely, Jürgen Debus, Wilfried De Neve, Marco Durante, Oliver Jäkel, Ramona Mayer, Roberto Orecchia, Richard Pötter, Stanislav Vatnitsky, William T Chu



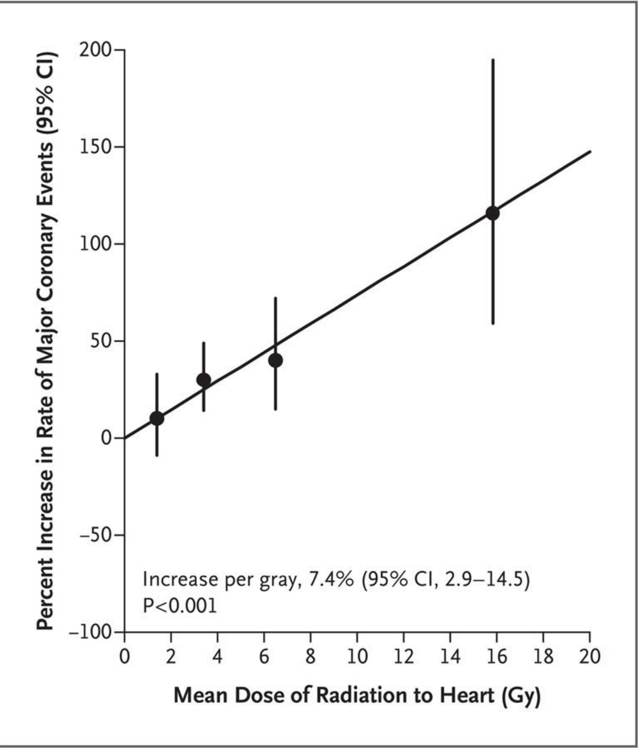
Particle therapy in pancreatic cancer



Durante et al., *Front. Oncol.*, 2015

Breast cancer

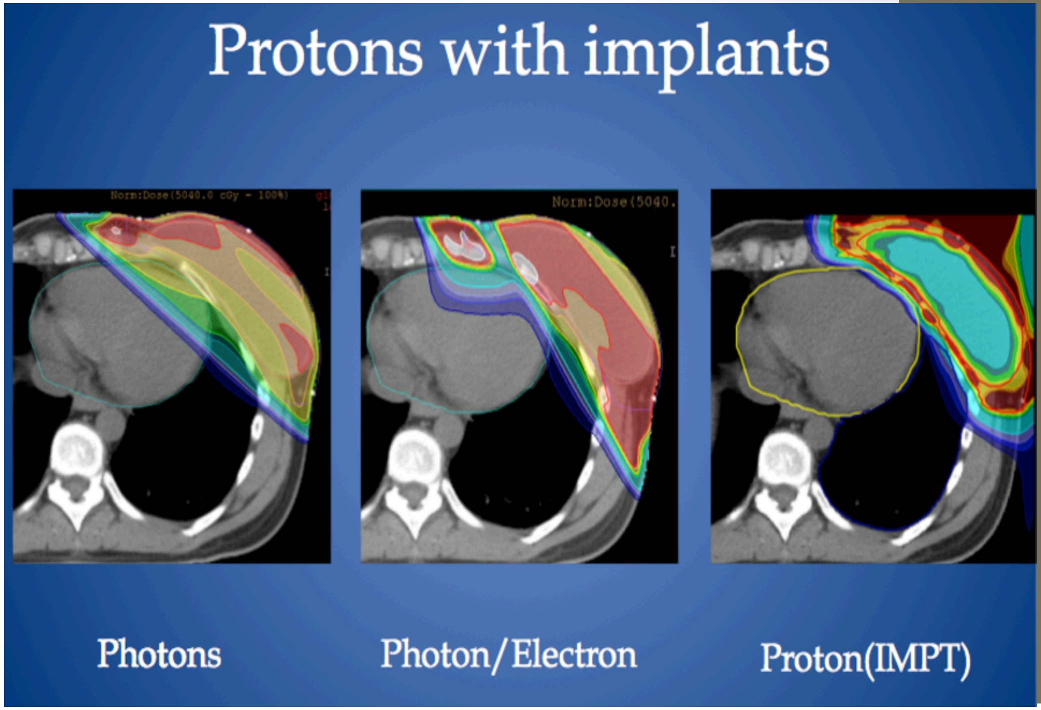
- 1st cancer in women (1 in 8)
- survival rate 80%
- high risk of late cardiac mortality



Increase per gray, 7.4% (95% CI, 2.9–14.5)
P<0.001

NEJM

14.3.2013

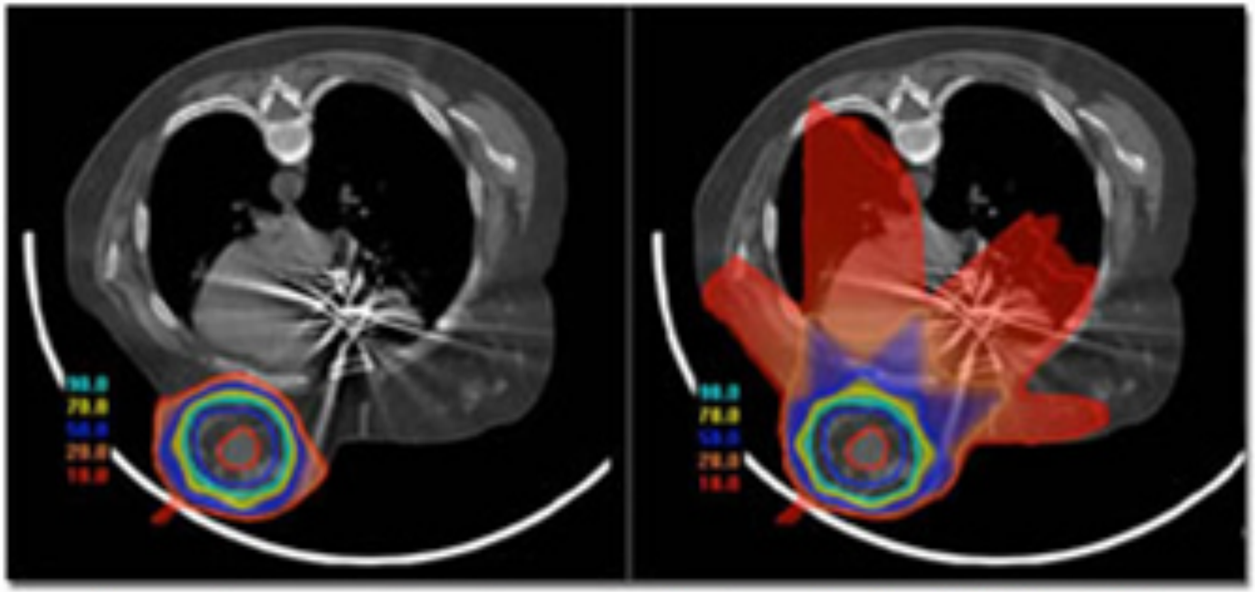


Protons with implants

Photons

Photon/Electron

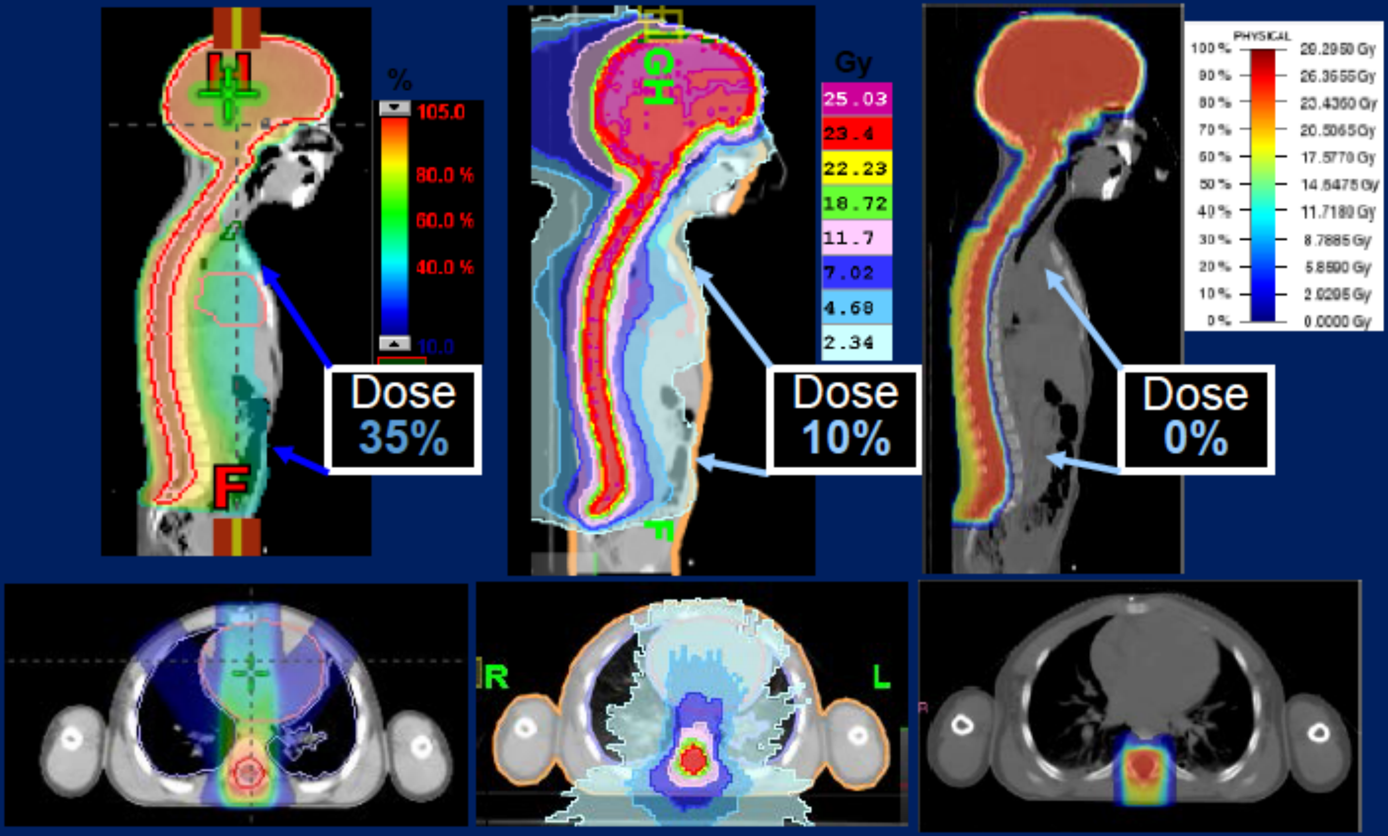
Proton(IMPT)



Breast cancer treatment: Proton left, IMRT right

TRATTAMENTO MEDULLOBLASTOMA PEDIATRICO

3DCRT **TOMO** **IMPT**



Advantages in summary

When compared to standard x-ray radiation:

1. Fewer short –and long-term side effects
2. Improved quality of life during and after treatment
3. Proven to be effective in adults and children
4. Reduces the likelihood of secondary tumors caused by treatment
5. Can be used to treat recurrent tumors even in patients who have already received radiation
6. Targets tumors and cancer cells with precision,

   reducing the risk of damage to surrounding healthy tissues and organs

drawbacks

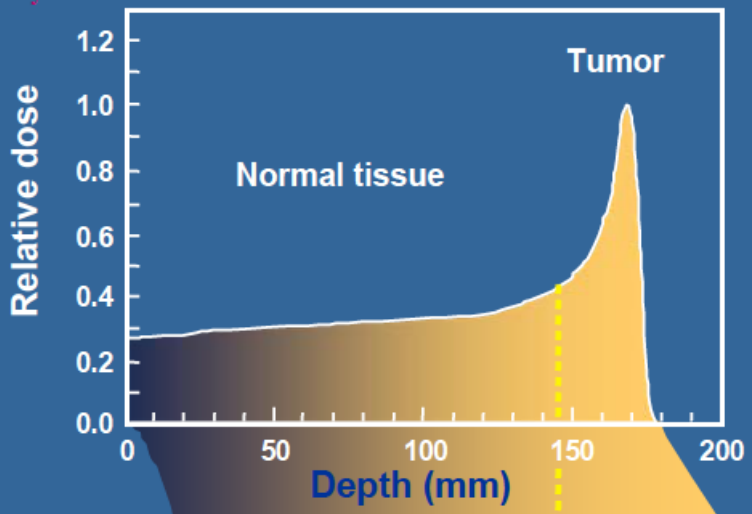
- **Limited availability-** This treatment requires highly specialized, expensive equipment. As a result, proton therapy is available at just a few medical centers in the United States

- **Higher expense-** Proton therapy costs more than conventional radiation therapy. equipment for production of protons, neutrons and heavy ions is considerably more expensive than standard radiotherapy equipment, both in capital costs and in maintenance and servicing costs.

In summary

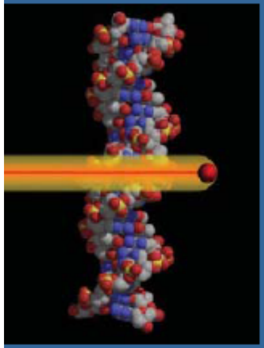
Graphics courtesy of

M. Belli



Durante & Loeffler,

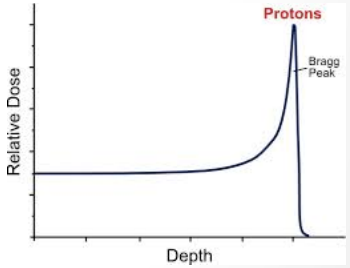
Nature Rev Clin Oncol 2010



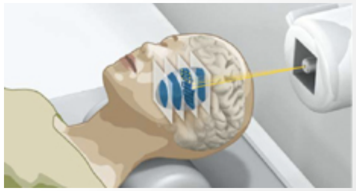
			Potential advantages
Energy	high	low	
LET	low	high	
Dose	low	high	High tumor dose, normal tissue sparing
RBE	≈ 1	> 1	Effective for radioresistant tumors
OER	≈ 3	< 3	Effective against hypoxic tumor cells
Cell-cycle dependence	high	low	Increased lethality in the target because cells in radioresistant (S) phase are sensitized
Fractionation dependence	high	low	Fractionation spares normal tissue more than tumor
Angiogenesis	Increased	Decreased	Reduced angiogenesis and metastatization
Cell migration	Increased	Decreased	

Finishing the job: how many things we could do with more nuclear physics….

- Ultrafast treatments (seconds)
- Moving targets (lung, abdomen….)
- Radiosurgery (single fractions for cancer and noncancer diseases)
- Oligometastasis (3-7 treated simultaneously)
- Image-guided adaptive treatments (hypoxia, cancer stem cells…..)



Bragg peak as the XXI century scapel



How?

Where ?

Synchrotron machine (CNAO)

Source & Linac

- 2 permanent magnet ECR sources
- 400 keV/u 4-rod type RFQ
- 20 MV IH-type drift tube linac (IH-DTL)

Synchrotron

Extraction

Treatment beams and rooms

Beam delivery system

Design Parameters II

Carbon (< 4 10^8 per spill)

	LEBT (C^{4+})	MEBT	SYNC	HEBT
Energy [MeV/u]	0.008	7	7-400	120-400
Imax [A]	0.16×10^{-3}	0.15×10^{-3}	1.5×10^{-3}	2×10^{-9}
Imin [A]	0.16×10^{-3}	15×10^{-6}	28×10^{-6}	4×10^{-12}
$\varepsilon_{rms,geo}$ [π mm mrad]	35	1.9	0.73-6.1	0.73-1.43(V)
$\varepsilon_{tot,geo}$ [π mm mrad]	180	9.4	3.66-30.4	3.66-7.14 (V) 5.0 (H)
Magnetic rigidity [T m]	0.039	0.76	0.76-6.34	3.25-6.34
$(\Delta p/p)_{tot}$	±1.0‰	±(1.2-2.0)‰	±(1.2-2.9)‰	±(0.4-0.6)‰

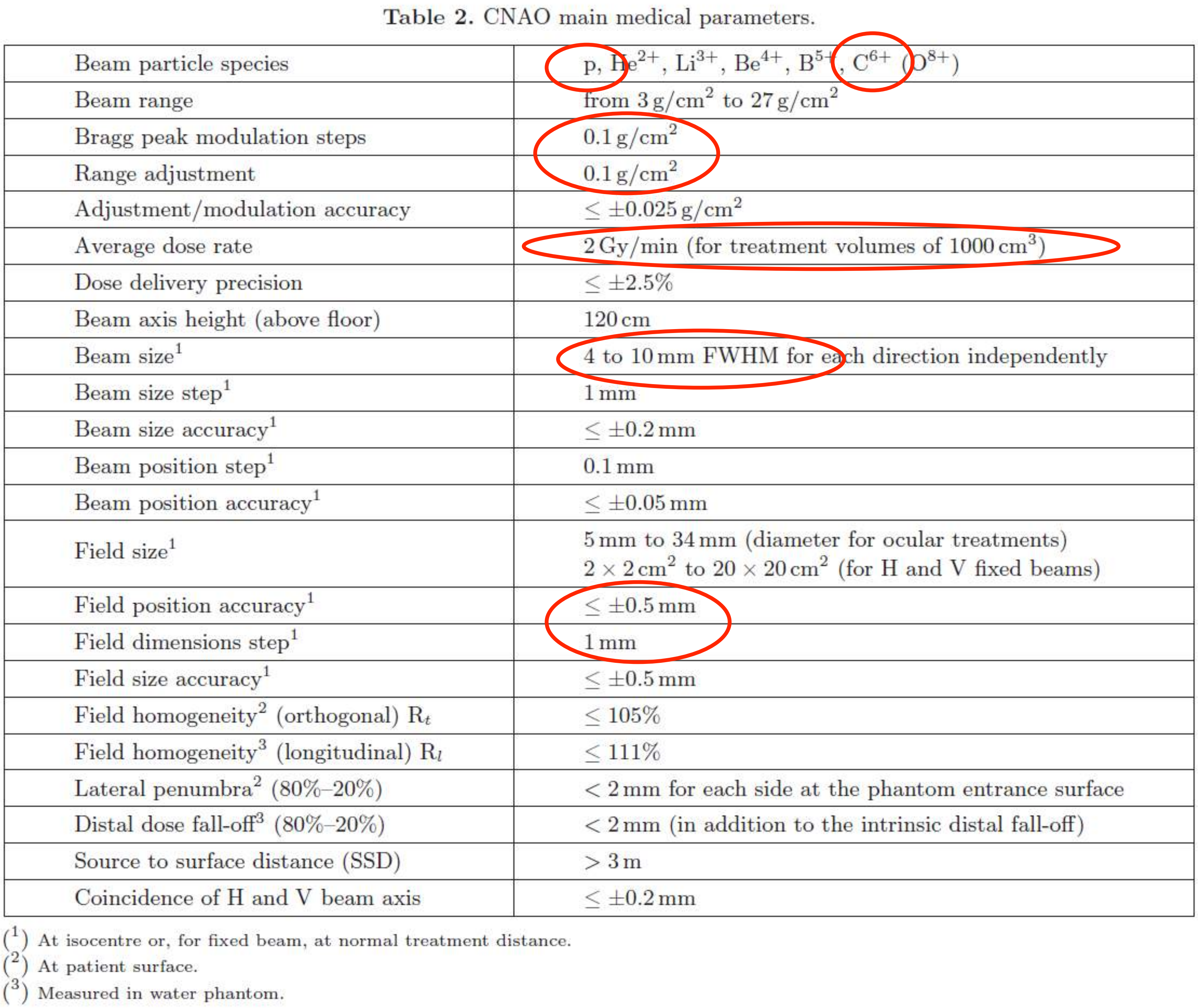
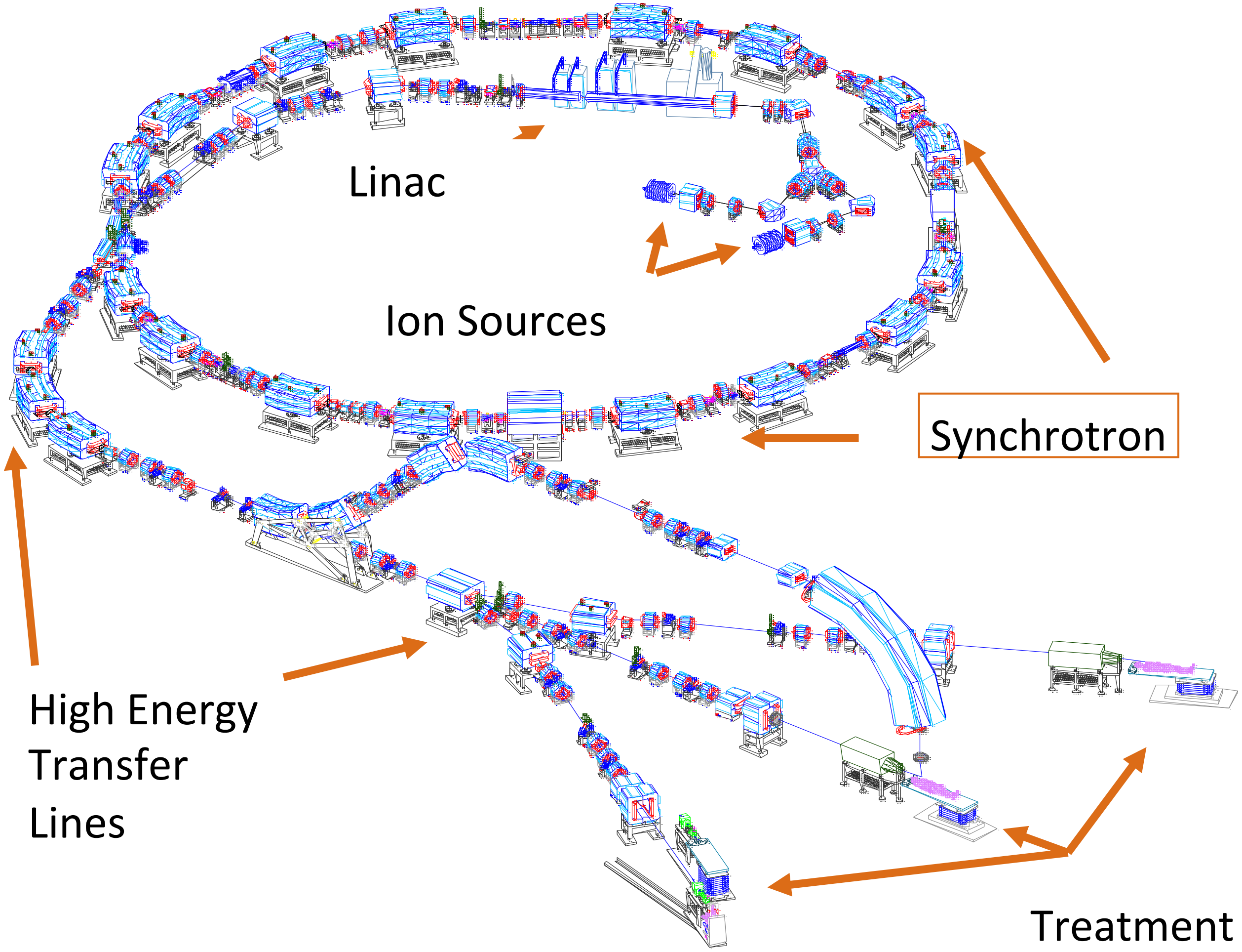


Table 2. CNAO main medical parameters.

Beam particle species	p, He^{2+}, Li^{3+}, Be^{4+}, B^{5+}, C^{6+} (O^{8+})
Beam range	from $3\,\mathrm{g/cm^2}$ to $27\,\mathrm{g/cm^2}$
Bragg peak modulation steps	$0.1\,\mathrm{g/cm^2}$
Range adjustment	$0.1\,\mathrm{g/cm^2}$
Adjustment/modulation accuracy	$\leq \pm 0.025\,\mathrm{g/cm^2}$
Average dose rate	2 Gy/min (for treatment volumes of $1000\,\mathrm{cm^3}$)
Dose delivery precision	$\leq \pm 2.5\%$
Beam axis height (above floor)	120 cm
Beam size[1]	4 to 10 mm FWHM for each direction independently
Beam size step[1]	1 mm
Beam size accuracy[1]	$\leq \pm 0.2$ mm
Beam position step[1]	0.1 mm
Beam position accuracy[1]	$\leq \pm 0.05$ mm
Field size[1]	5 mm to 34 mm (diameter for ocular treatments) $2 \times 2\,\mathrm{cm^2}$ to $20 \times 20\,\mathrm{cm^2}$ (for H and V fixed beams)
Field position accuracy[1]	$\leq \pm 0.5$ mm
Field dimensions step[1]	1 mm
Field size accuracy[1]	$\leq \pm 0.5$ mm
Field homogeneity[2] (orthogonal) R_t	$\leq 105\%$
Field homogeneity[3] (longitudinal) R_l	$\leq 111\%$
Lateral penumbra[2] (80%–20%)	< 2 mm for each side at the phantom entrance surface
Distal dose fall-off[3] (80%–20%)	< 2 mm (in addition to the intrinsic distal fall-off)
Source to surface distance (SSD)	> 3 m
Coincidence of H and V beam axis	$\leq \pm 0.2$ mm

(1) At isocentre or, for fixed beam, at normal treatment distance.
(2) At patient surface.
(3) Measured in water phantom.

The accelerator



Linac

Ion Sources

Synchrotron

High Energy
Transfer
Lines

Treatment
Rooms

Compact design

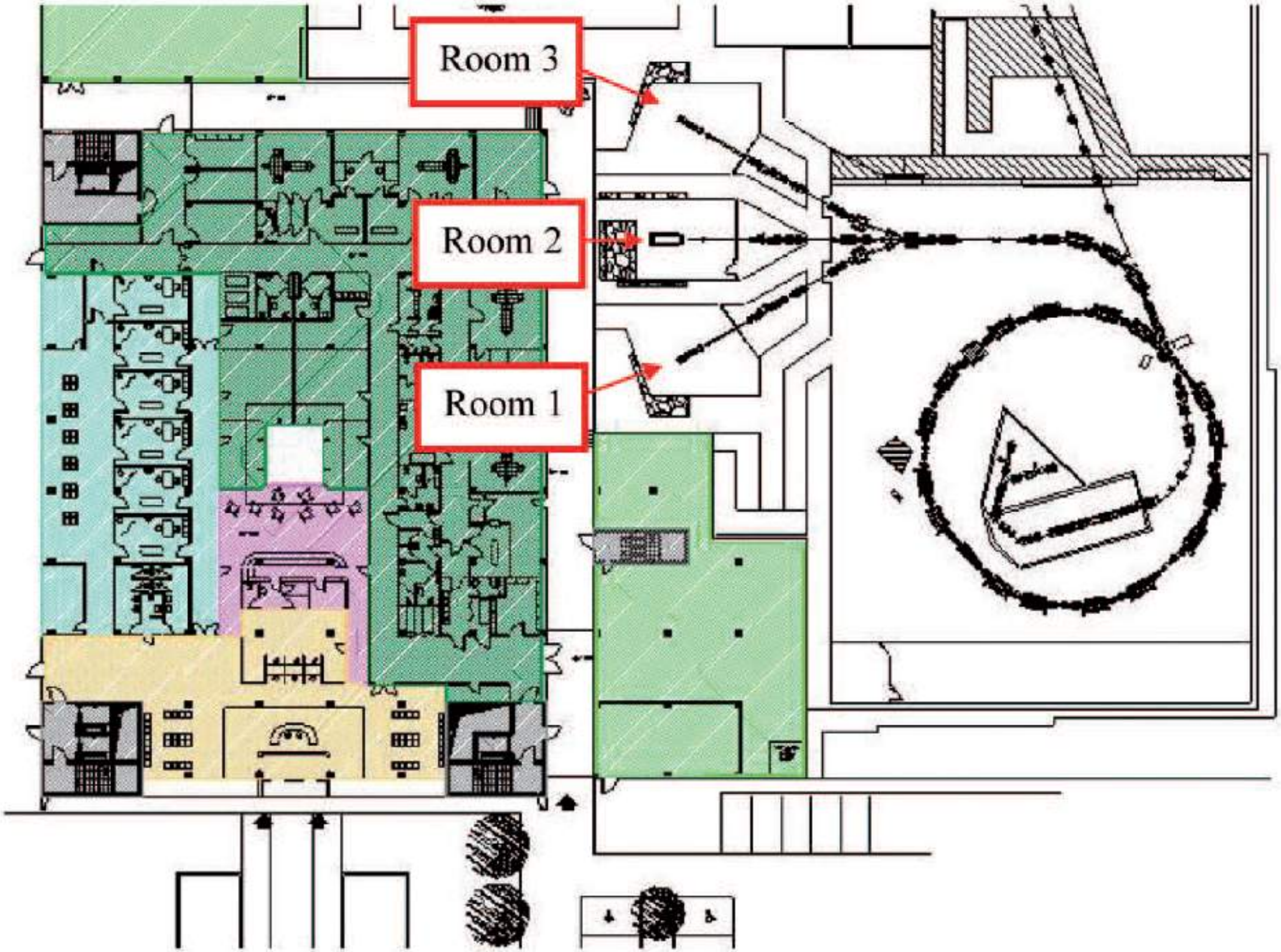
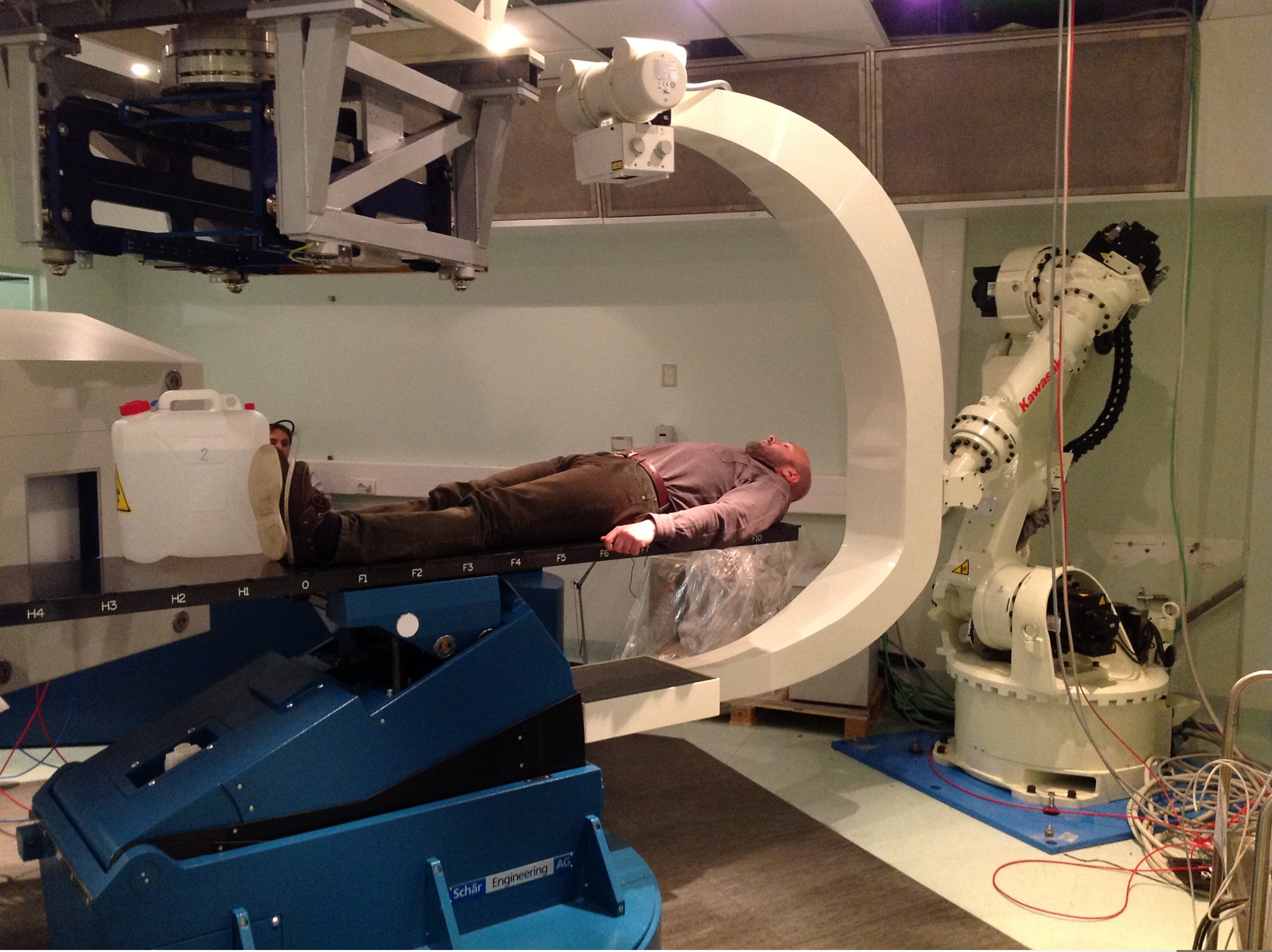


Fig. 8. Underground floor layout of CNAO complex, showing the accelerators and the treatment rooms.

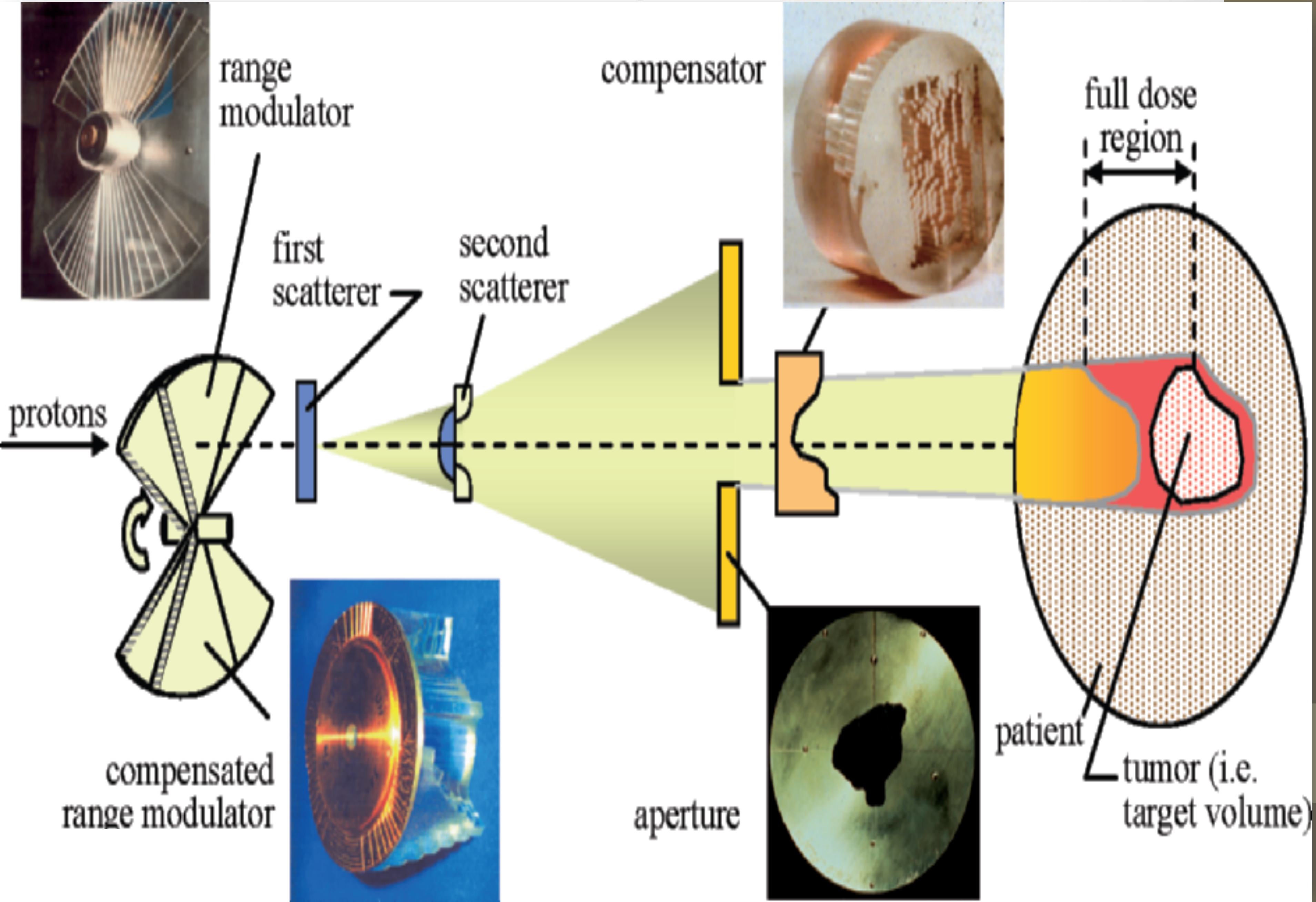

DANFYSIK
DANFYSIK

Patient positioning

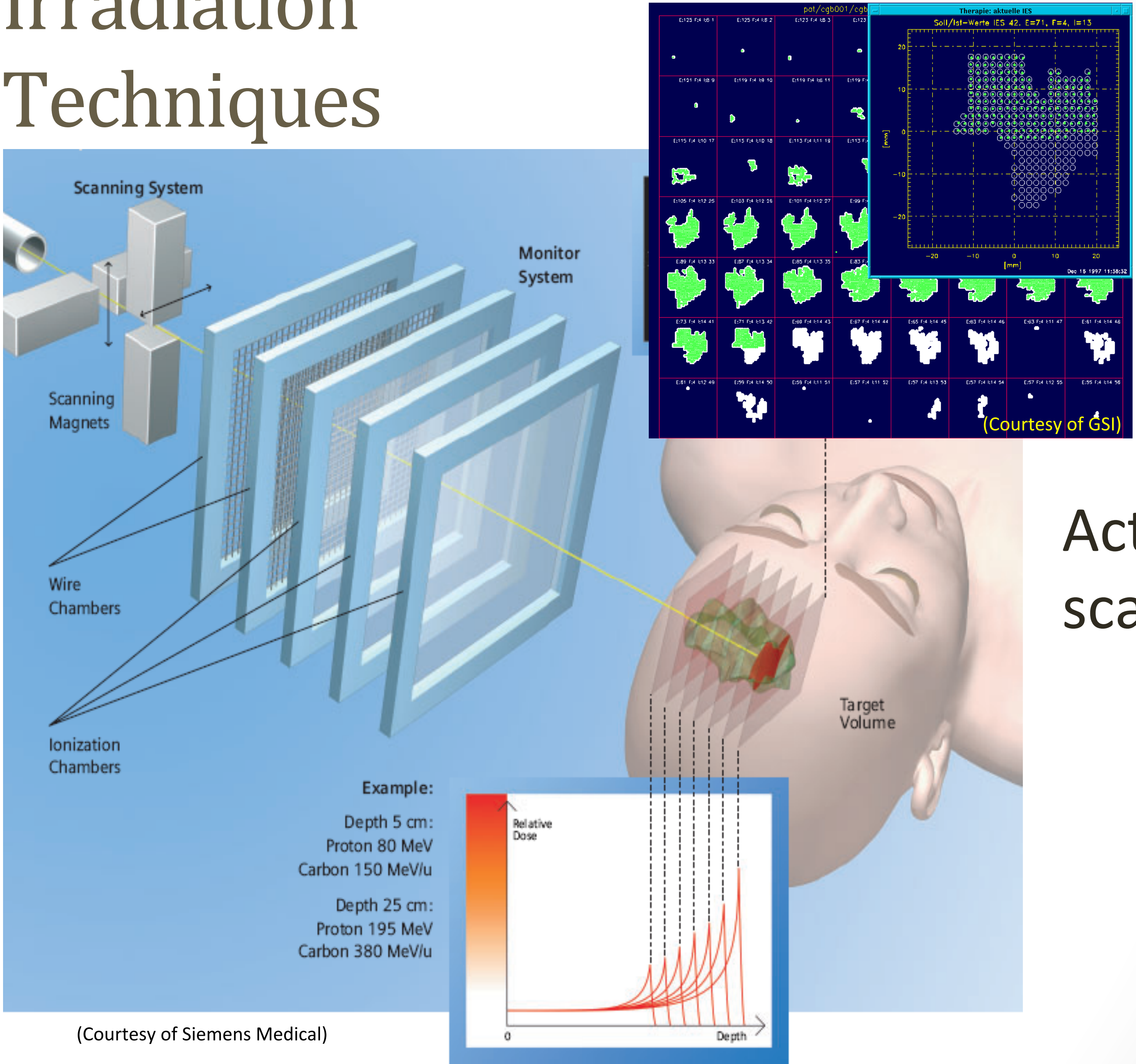
- Couch platform rides on air cushion
- IR optical tracking and lasers
  - Later may use x-rays or CT
- Some pre-positioning outside of room
- Therapists dont like to make patients wait
- Alignment and Prep takes a long time


2
H4
H3
H2
H1
0
F1
F2
F3
F4
F5
F6
F10
Kawasaki
Schär Engineering AG

Passive scattering



Irradiation Techniques



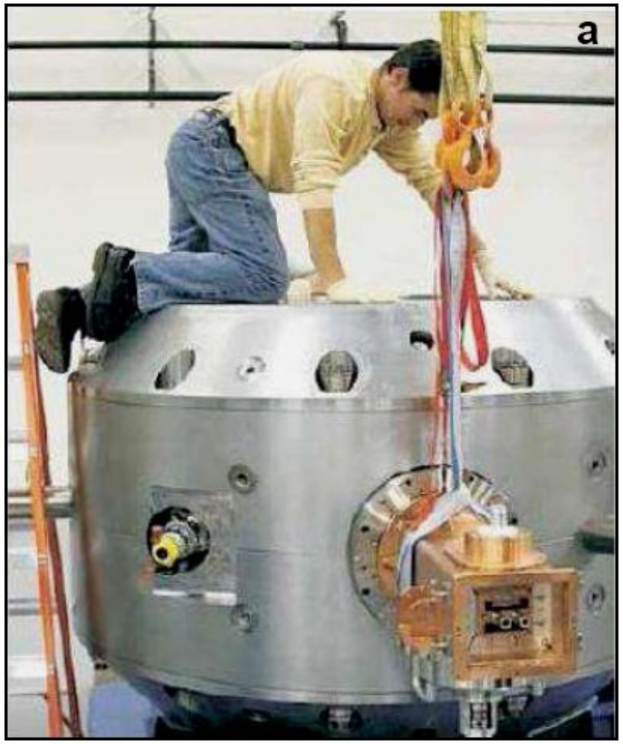
(Courtesy of GSI)

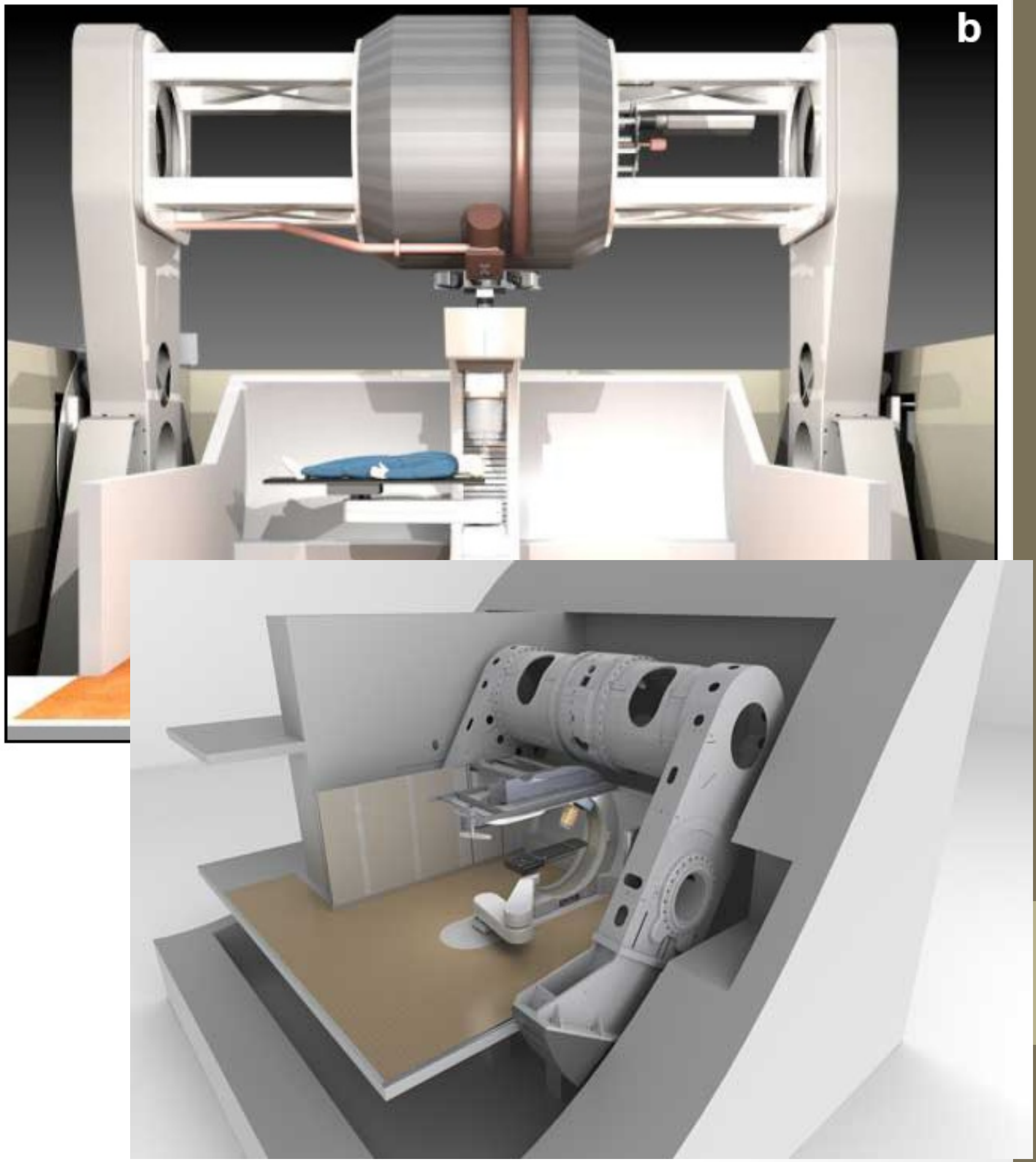
(Courtesy of Siemens Medical)

Active scanning

Coming up: single room facility

250 MeV synchrocyclotron rotating around the patient



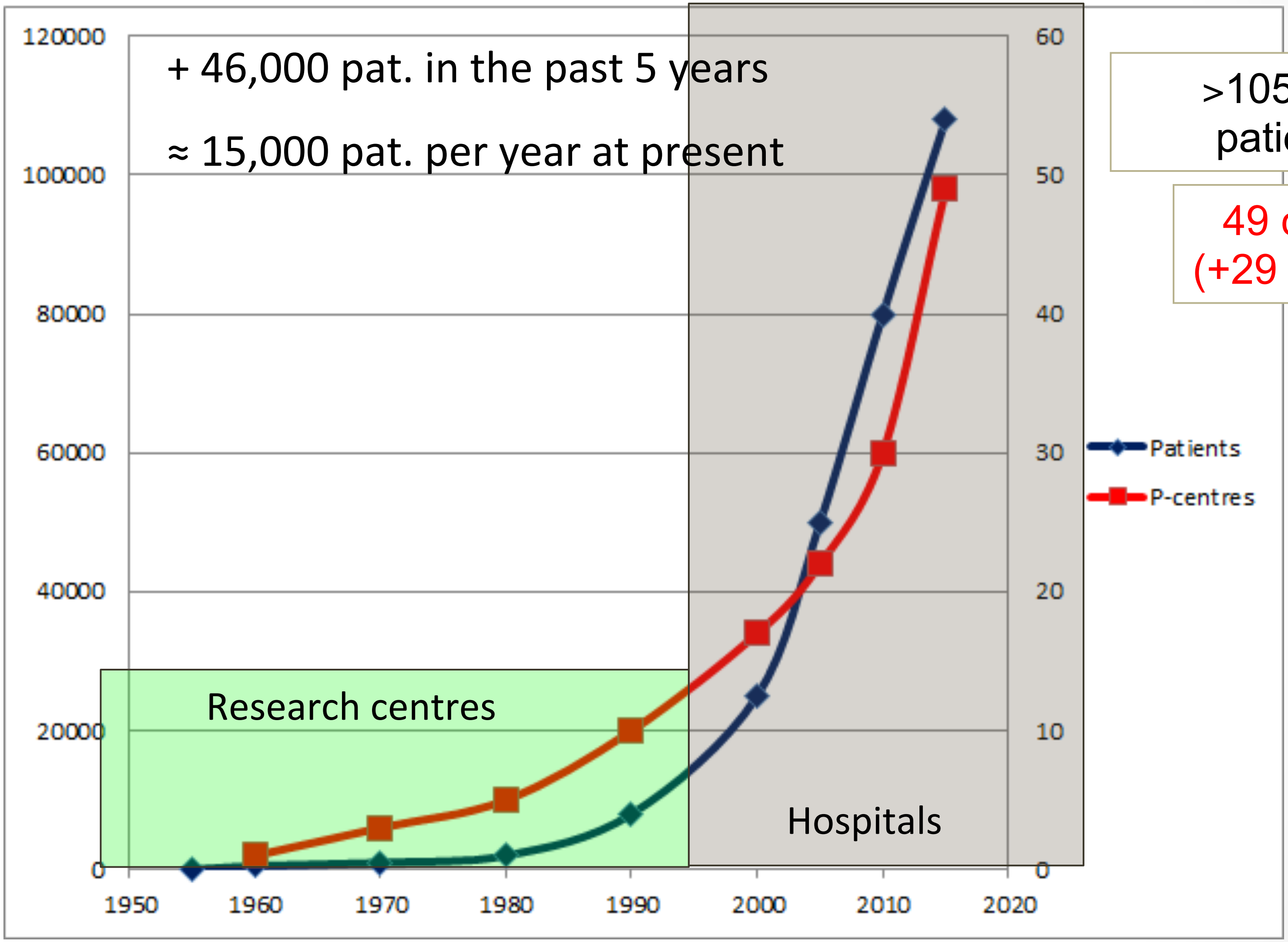


MEVION S250

Superconducting SC
Diameter 1.8 m

Protontherapy in the world

(www.ptcog.psi.ch)



+ 46,000 pat. in the past 5 years

≈ 15,000 pat. per year at present

>105.000 patients

49 centres (+29 planned)

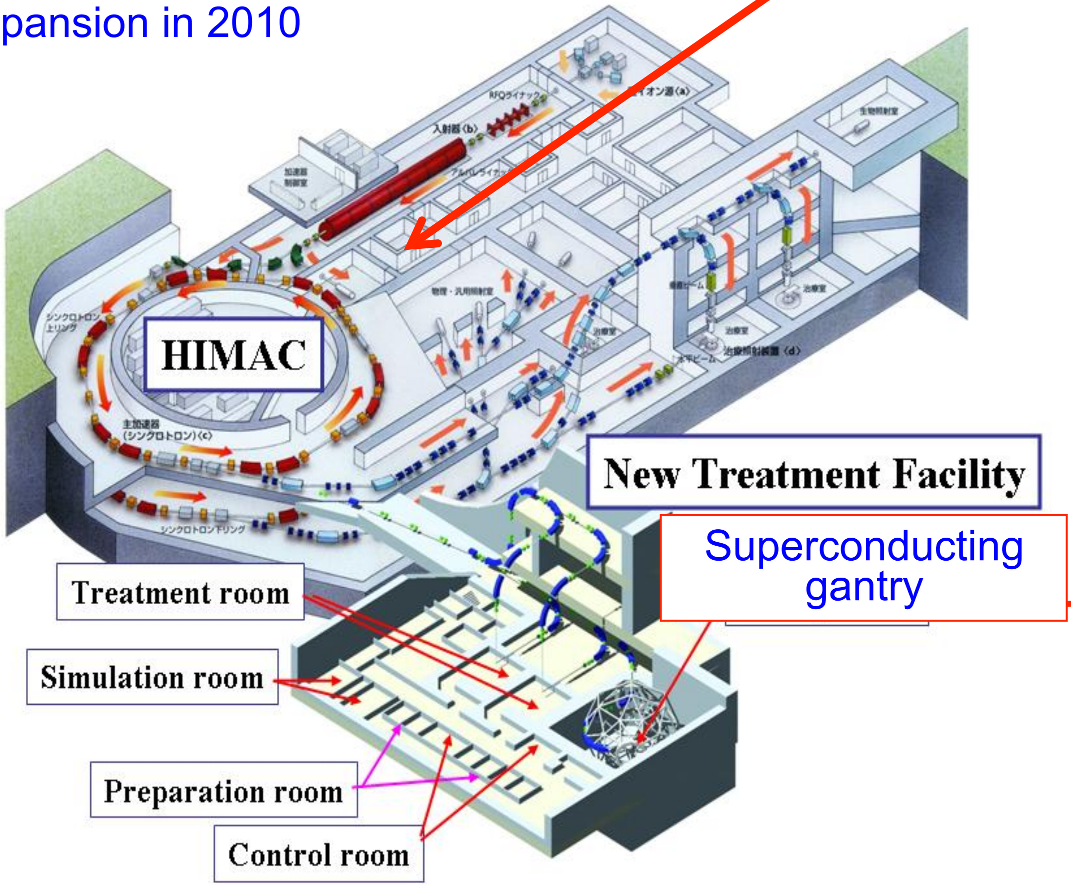
Carbon Ions: >15.000 patients; 8 centres (+4 in construction)

Carbon Ion facilities

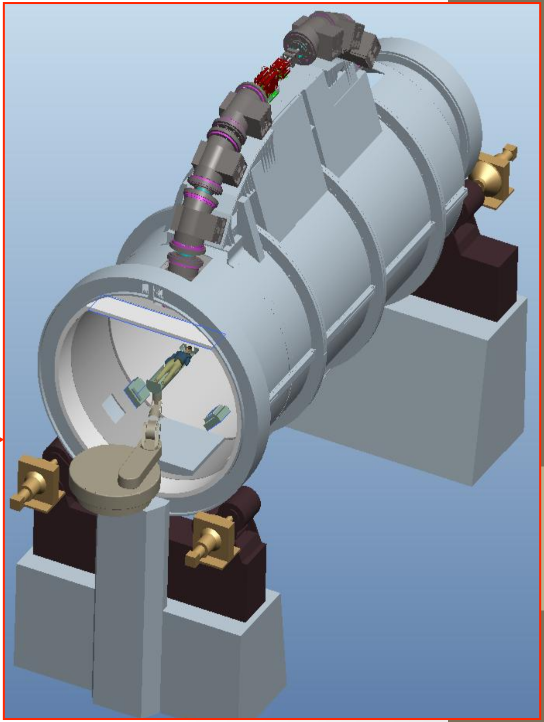
HIMAC
Heavy Ion Medical Accelerator in Chiba
(First patient in 1995)

2 synchrotrons 800 MeV/u, therapy and nuclear physics

Expansion in 2010



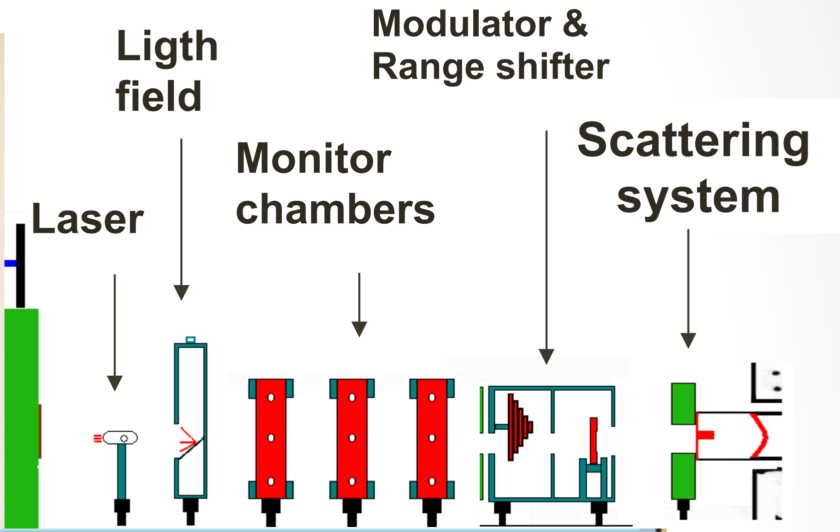
Superconducting gantry



Hadron therapy in Italy

- **CATANA – INFN LNS – SICILY**
  - **Active since 2002**
  - **Proton beam for eye treatment (Cyclotron < 60 MeV)**
- **PROTON THERAPY CENTER - TRENTO**
  - **Active since 2015**
  - **Proton beam full body treatment (Cyclotron 60-230 MeV)**
- **CNAO – PAVIA**
  - **Active since 2011**
  - **Proton and Heavy Ion (C) beam**
  - **Realized by INFN**

CATANA proton therapy beam line



Laser

Ligth field

Monitor chambers

Modulator & Range shifter

Scattering system

ADROTERAPIA DEI MELANOMI OCULARI
L'ESPERIENZA CLINICA DEL GRUPPO DI CATANIA

G. Di Franco[1], G. Privitera[1], C. Spatola[1], G.C. Ettorre[1],
L. Raffaele[1], V. Salamone[1], L.M. Valastro[1], A. Reibaldi[2], J. Ott[2]
G.A.P. Cirrone[3], G. Cuttone[3], M. Lattuada[3], D. Rifuggiato[3], S. Pittera[4], S. Lo Nigro[4]

[1] *Struttura Complessa di Radiodiagnostica e Radioterapia, Az. Ospedaliero-Universitaria di Catania*
[2] *Clinica Oculistica, Azienda Ospedaliero-Universitaria Policlinico di Catania*
[3] *Laboratori Nazionali del Sud, Istituto Nazionale di Fisica Nucleare*
[4] *CSFNSM, Centro Siciliano di Fisica Nucleare e Struttura della Materia, Catania*

Pazienti trattati dal 2002 al 2015

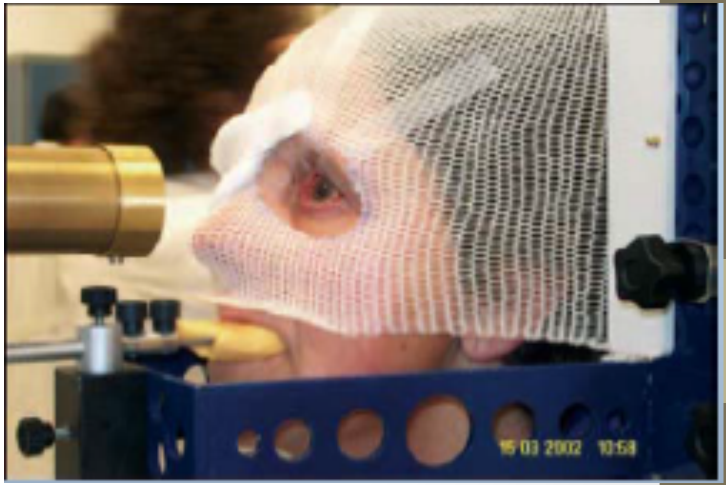
SOPRAVVIVENZA		
Total Number of patients	363	
Deaths	6	
	Metastatis	5
	Other	1
Eye retention rate	95 %	
Surviving	98 %	
LOCAL CONTROL	95 %	

Salvato l’occhio al 95 % dei pazienti

Asportato l’occhio per:

- perforazione della cornea
- progressione locale del tumore
- danni radio indotti

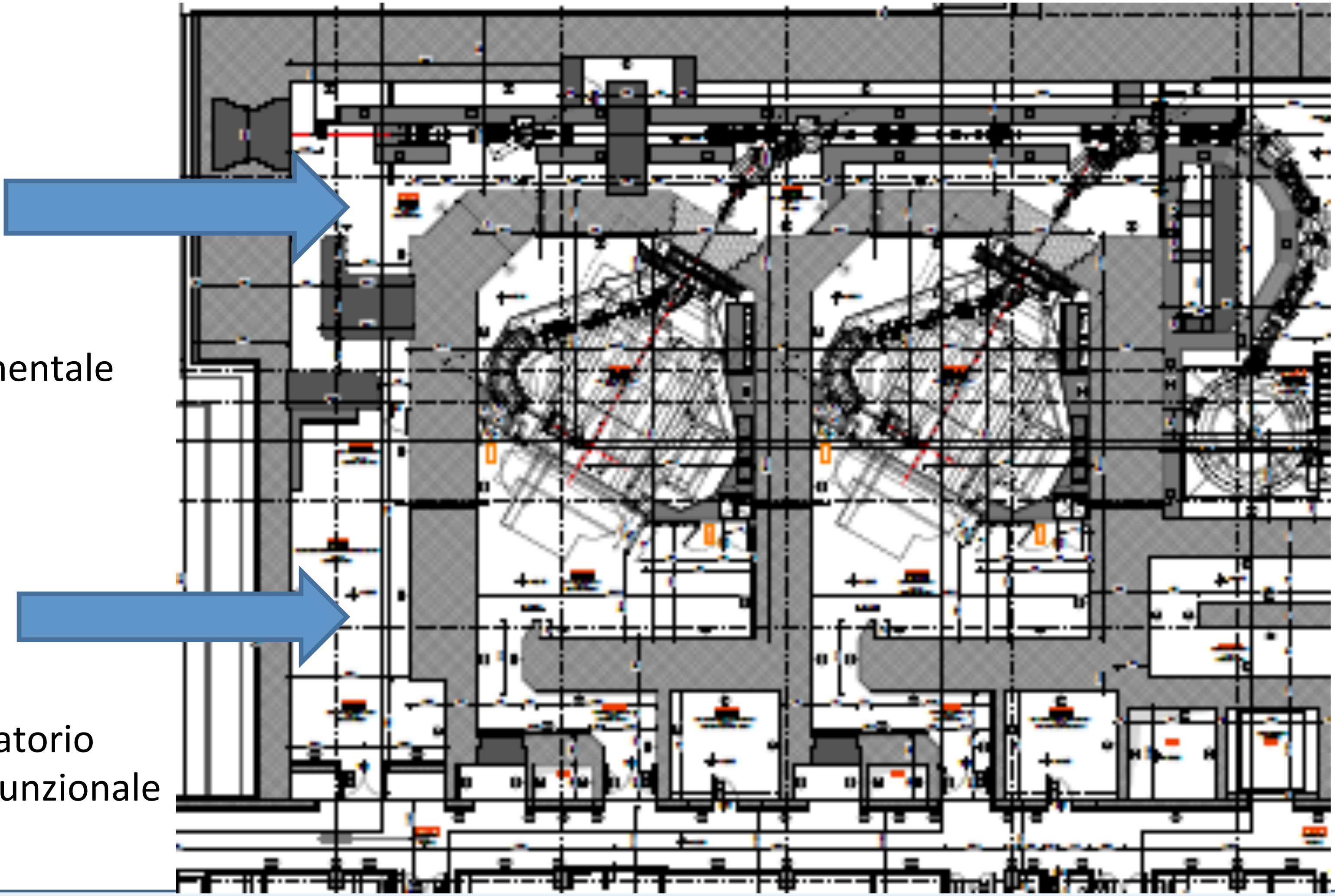
Insorte metastasi in alcuni pazienti di cui 6 deceduti



Proton Therapy - Trento

- APSS
  - Active from 2015
  - About 50 patient treated
  - Cyclotron 60-230 MeV produced and maintained by IBA
  - Cost about 110 M€

Experimental cave



Sala sperimentale

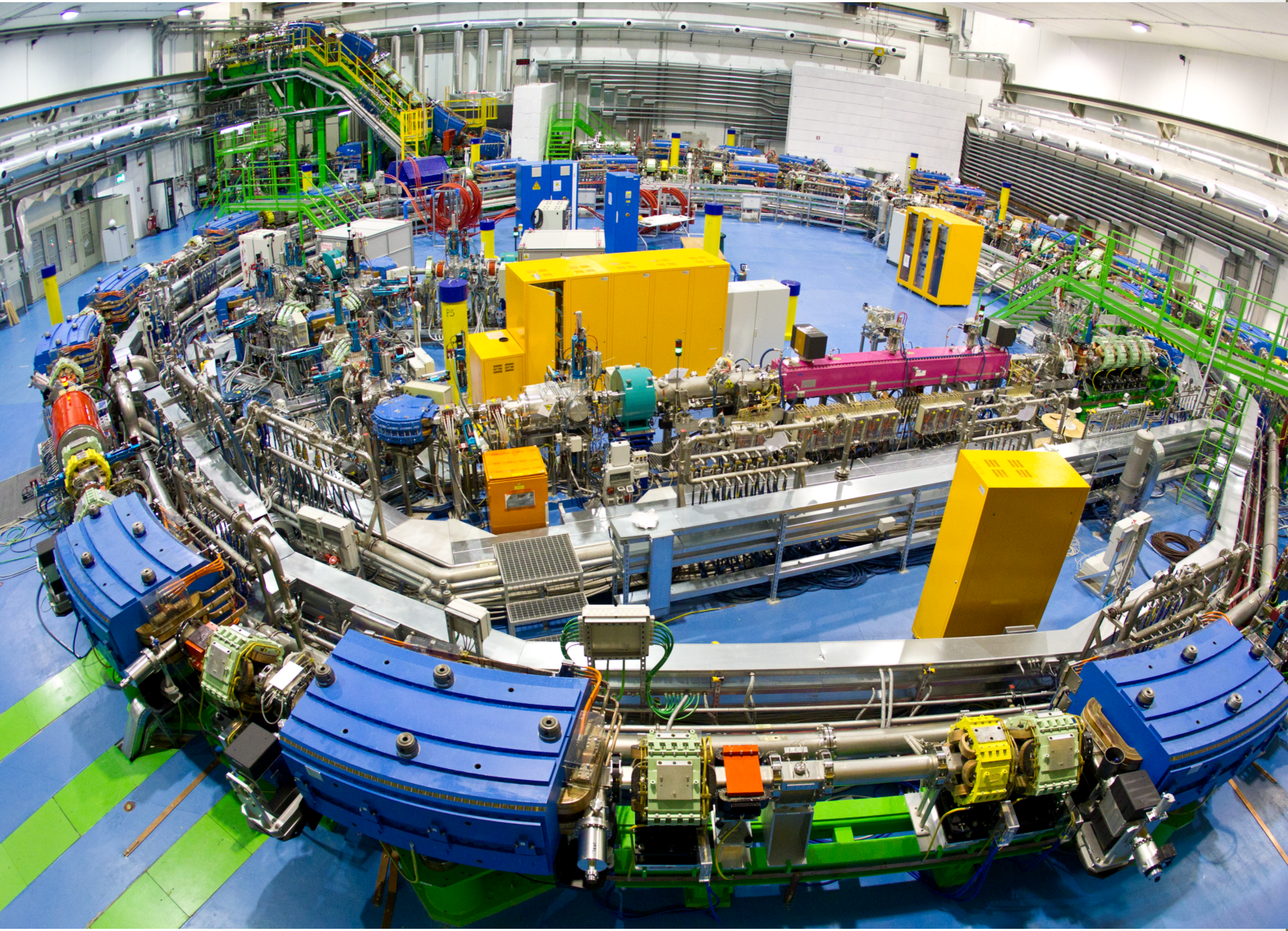
Laboratorio multifunzionale

CNAO - Pavia

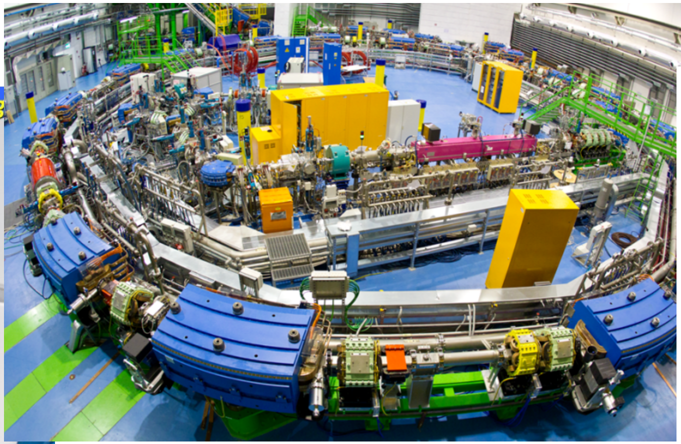
- Active from 2011
- About 650 patient treated both with protons and Carbon-ions
- Synchrotron designed, realized and commissioned by INFN
- Cost about 150-200 M€

CNAO - Pavia

Synchrotron for protons and Carbon ions



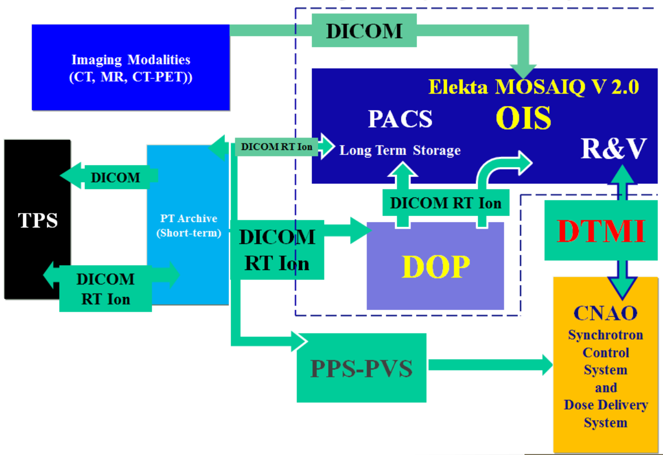
Much more than … "just" … an accelerator



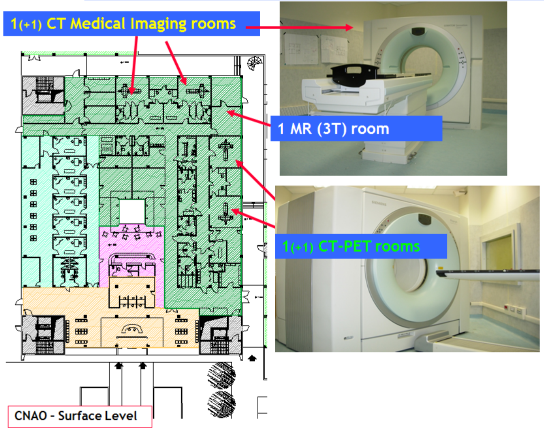
High precision devices for patient positioning

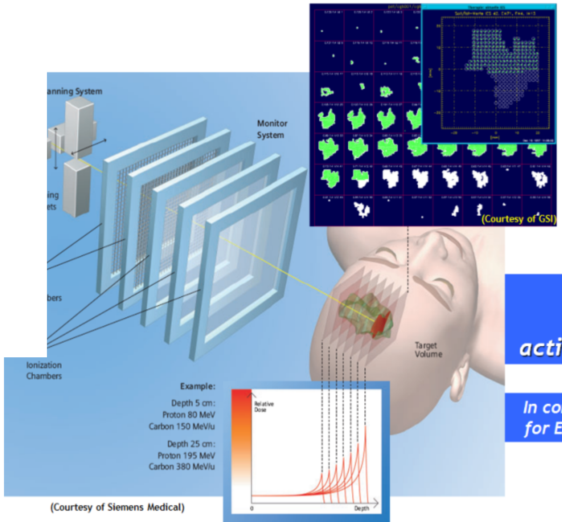
Collaboration CNAO-PoliMi

Oncological Information System



Advanced Medical Imaging Modalities (fusion sw)





Example:
Depth 5 cm:
Proton 80 MeV
Carbon 150 MeV/u
Depth 25 cm:
Proton 195 MeV
Carbon 380 MeV/u

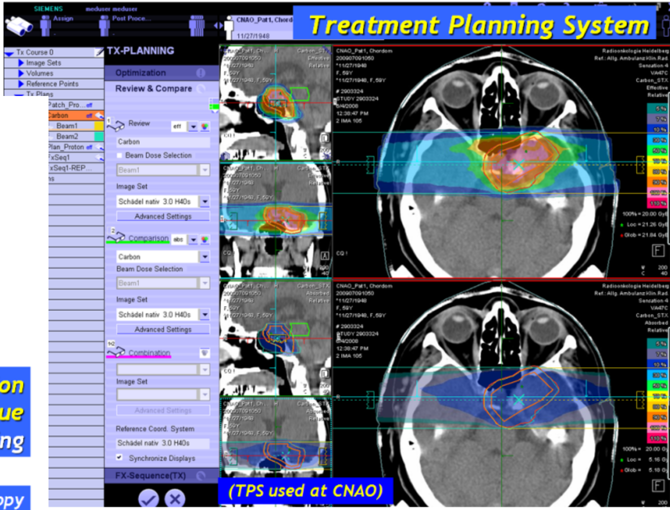
(Courtesy of GSI)

(Courtesy of Siemens Medical)

Irradiation technique active scanning

In construction copy for EBG-MedAustron

Treatment Planning System



(TPS used at CNAO)

Le fasi del CNAO

Fase 0: organizzazione → Anni: 2002 - 2004

Fase 1: costruzione (INFN) → Anni: 2005 - 2010

Fase 2: sperimentazione → Anni: 2010 - 2013

Fase 3: funzionamento → Anni: 2014 - …

Il Consiglio di Indirizzo

Soci Fondatori:

Fondazione Policlinico Ospedale Maggiore - Milano

Fondazione Istituto Neurologico C. Besta - Milano

Fondazione Istituto Nazionale dei Tumori - Milano

Istituto Europeo di Oncologia - Milano

Fondazione Policlinico San Matteo - Pavia

Fondazione TERA - Novara

Partecipanti Istituzionali:

Istituto Nazionale di Fisica Nucleare

Università di Milano

Politecnico di Milano

Università di Pavia

Comune di Pavia

Partecipanti:

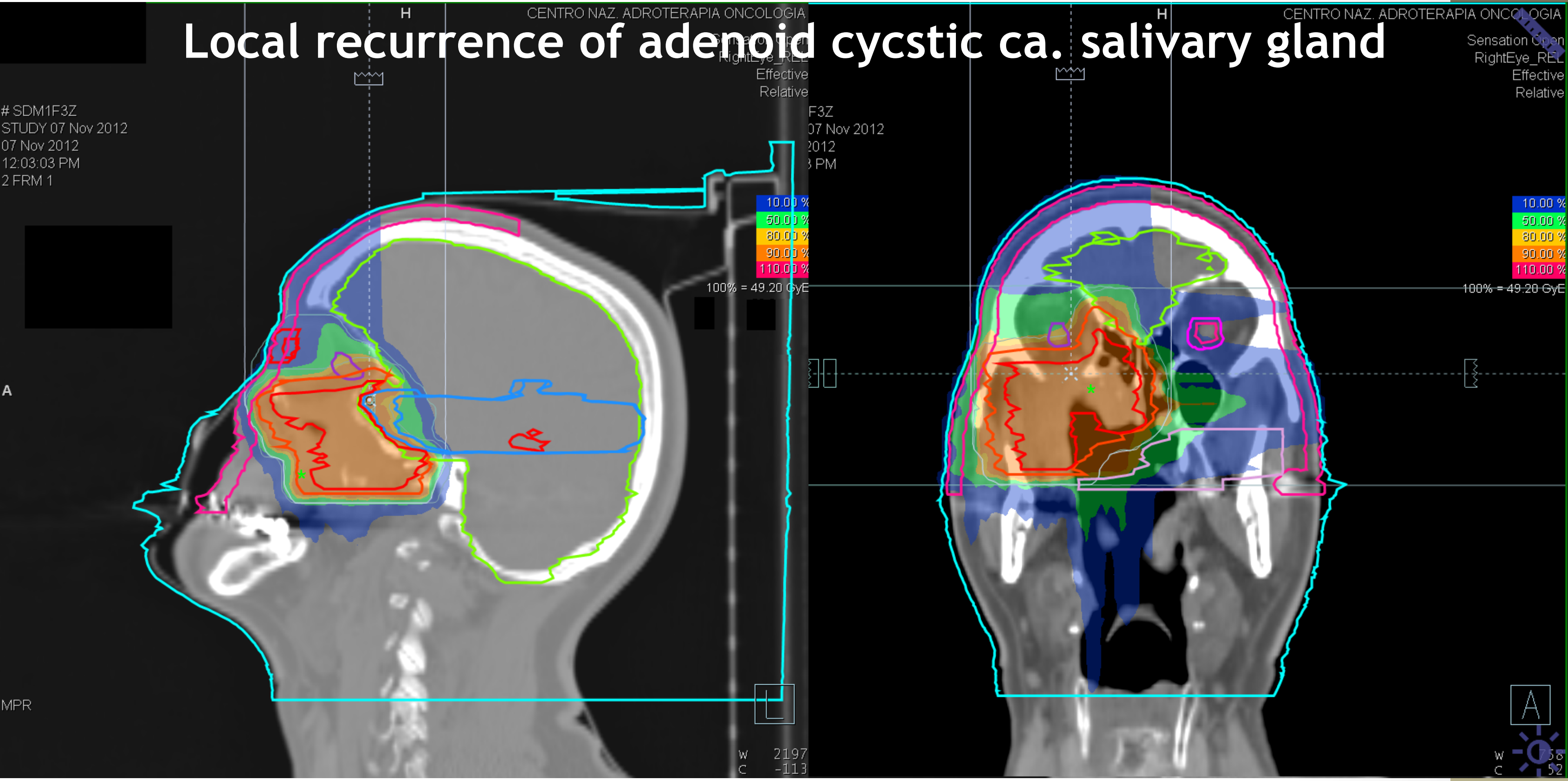
Fondazione Cariplo

Ministero della Salute

22 Settembre2011
Primo trattamento con protoni al CNAO

[redacted]

13 Novembre 2012: primo paziente al CNAO con ioni carbonio



Local recurrence of adenoid cycstic ca. salivary gland

[redacted]

[redacted]

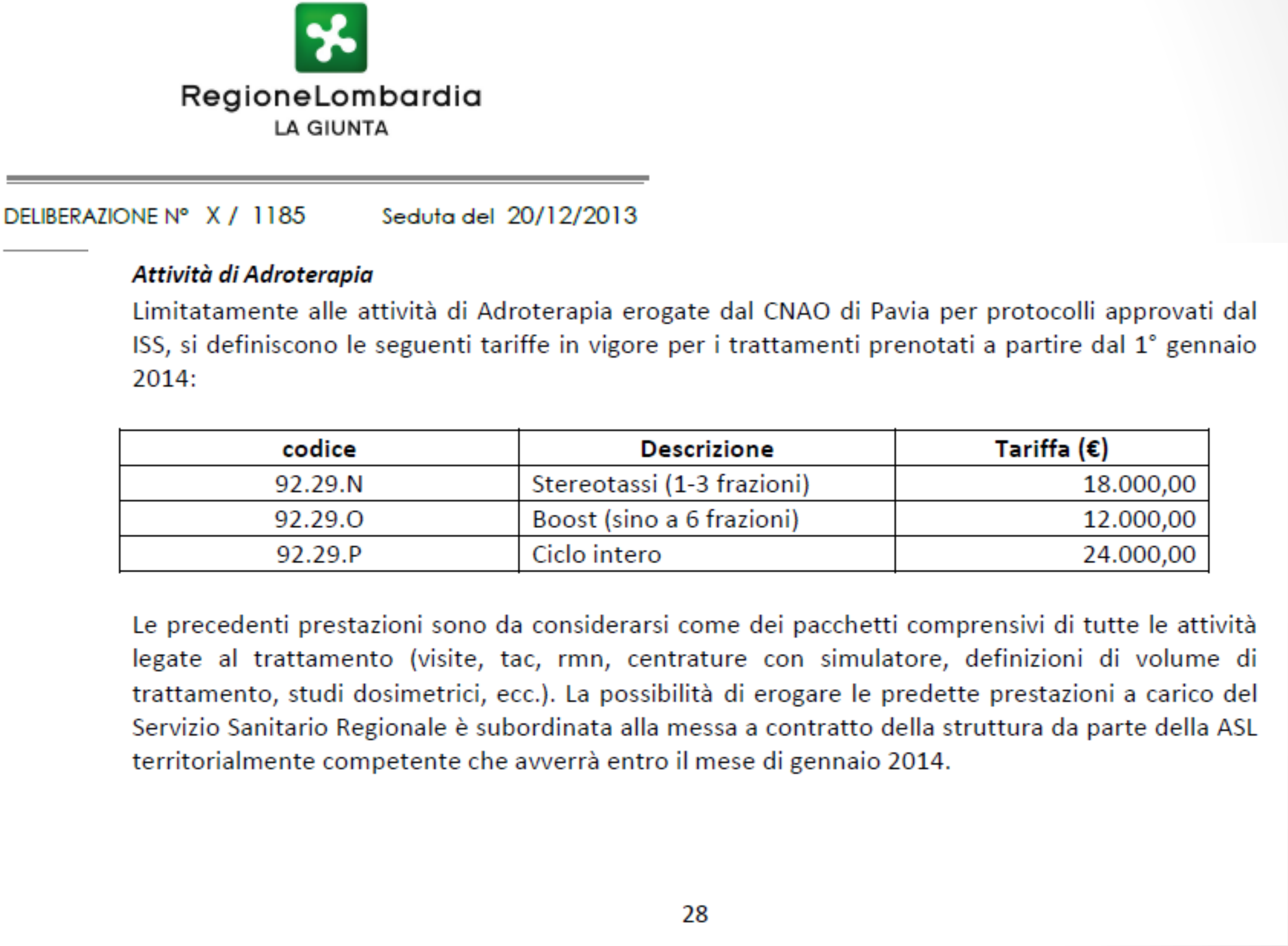
[redacted]

[redacted]

12 fractions 4.1 GyE , 4 fractions per week, 49.2 GyE total dose. Boost of 4 fractions in case of good tolerance.

3 fields of IMPT

Le tariffe di adroterapia



RegioneLombardia
LA GIUNTA

DELIBERAZIONE N° X / 1185 Seduta del 20/12/2013

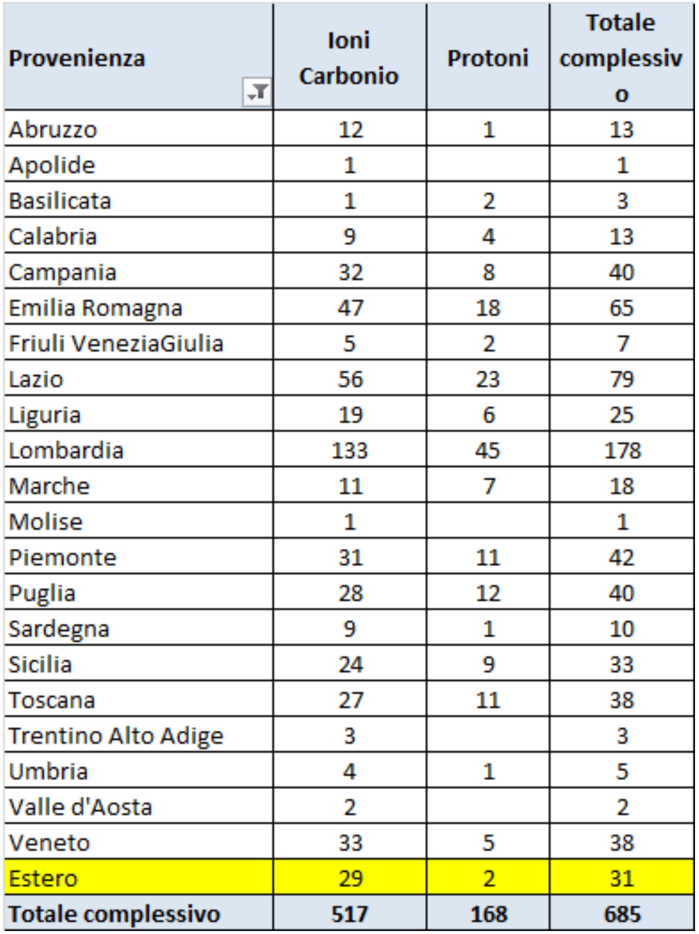
Attività di Adroterapia

Limitatamente alle attività di Adroterapia erogate dal CNAO di Pavia per protocolli approvati dal ISS, si definiscono le seguenti tariffe in vigore per i trattamenti prenotati a partire dal 1° gennaio 2014:

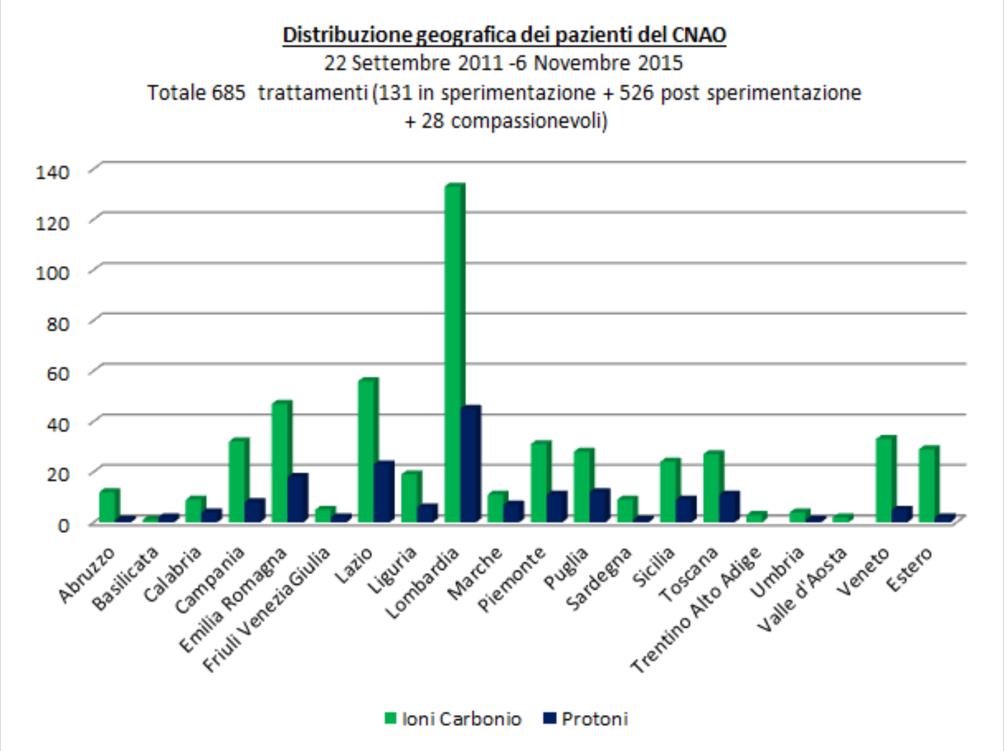
codice	**Descrizione**	**Tariffa (€)**
92.29.N	Stereotassi (1-3 frazioni)	18.000,00
92.29.O	Boost (sino a 6 frazioni)	12.000,00
92.29.P	Ciclo intero	24.000,00

Le precedenti prestazioni sono da considerarsi come dei pacchetti comprensivi di tutte le attività legate al trattamento (visite, tac, rmn, centrature con simulatore, definizioni di volume di trattamento, studi dosimetrici, ecc.). La possibilità di erogare le predette prestazioni a carico del Servizio Sanitario Regionale è subordinata alla messa a contratto della struttura da parte della ASL territorialmente competente che avverrà entro il mese di gennaio 2014.

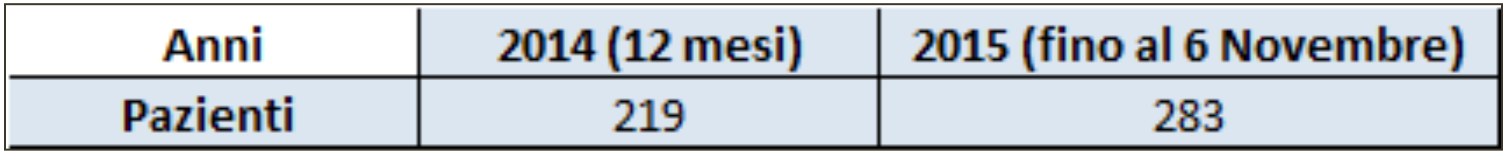
Pazienti trattati al CNAO



Provenienza	Ioni Carbonio	Protoni	Totale complessivo
Abruzzo	12	1	13
Apolide	1		1
Basilicata	1	2	3
Calabria	9	4	13
Campania	32	8	40
Emilia Romagna	47	18	65
Friuli VeneziaGiulia	5	2	7
Lazio	56	23	79
Liguria	19	6	25
Lombardia	133	45	178
Marche	11	7	18
Molise	1		1
Piemonte	31	11	42
Puglia	28	12	40
Sardegna	9	1	10
Sicilia	24	9	33
Toscana	27	11	38
Trentino Alto Adige	3		3
Umbria	4	1	5
Valle d'Aosta	2		2
Veneto	33	5	38
Estero	29	2	31
Totale complessivo	**517**	**168**	**685**



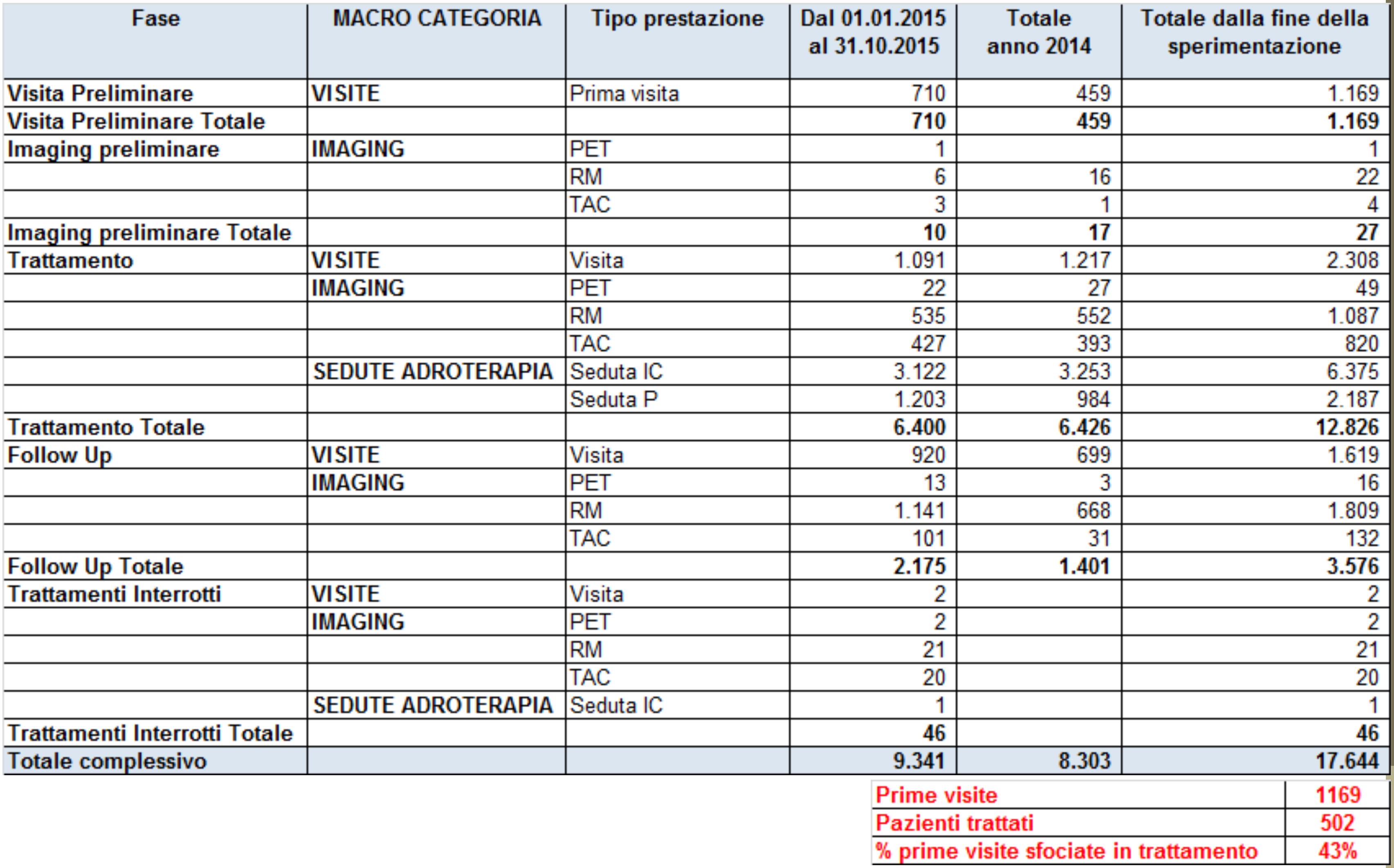
Distribuzione geografica dei pazienti del CNAO
22 Settembre 2011 -6 Novembre 2015
Totale 685 trattamenti (131 in sperimentazione + 526 post sperimentazione + 28 compassionevoli)



Anni	2014 (12 mesi)	2015 (fino al 6 Novembre)
Pazienti	219	283

Previsione chiusura 2015: **310 pazienti** → + 42 % rispetto al 2014

Prestazioni sanitarie al CNAO: 2015 vs 2014

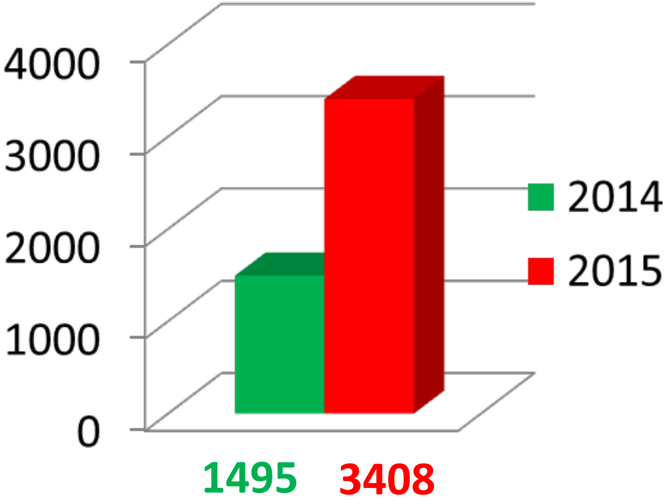


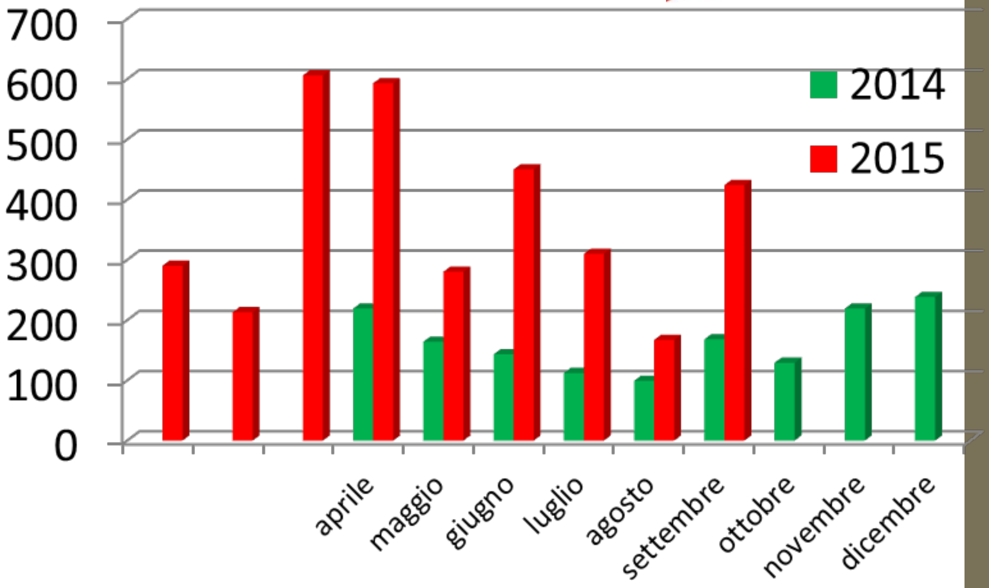
Fase	MACRO CATEGORIA	Tipo prestazione	Dal 01.01.2015 al 31.10.2015	Totale anno 2014	Totale dalla fine della sperimentazione
Visita Preliminare	**VISITE**	Prima visita	710	459	1.169
Visita Preliminare Totale			**710**	**459**	**1.169**
Imaging preliminare	**IMAGING**	PET	1		1
		RM	6	16	22
		TAC	3	1	4
Imaging preliminare Totale			**10**	**17**	**27**
Trattamento	**VISITE**	Visita	1.091	1.217	2.308
	IMAGING	PET	22	27	49
		RM	535	552	1.087
		TAC	427	393	820
	SEDUTE ADROTERAPIA	Seduta IC	3.122	3.253	6.375
		Seduta P	1.203	984	2.187
Trattamento Totale			**6.400**	**6.426**	**12.826**
Follow Up	**VISITE**	Visita	920	699	1.619
	IMAGING	PET	13	3	16
		RM	1.141	668	1.809
		TAC	101	31	132
Follow Up Totale			**2.175**	**1.401**	**3.576**
Trattamenti Interrotti	**VISITE**	Visita	2		2
	IMAGING	PET	2		2
		RM	21		21
		TAC	20		20
	SEDUTE ADROTERAPIA	Seduta IC	1		1
Trattamenti Interrotti Totale			**46**		**46**
Totale complessivo			**9.341**	**8.303**	**17.644**

Prime visite	**1169**
Pazienti trattati	**502**
% prime visite sfociate in trattamento	**43%**

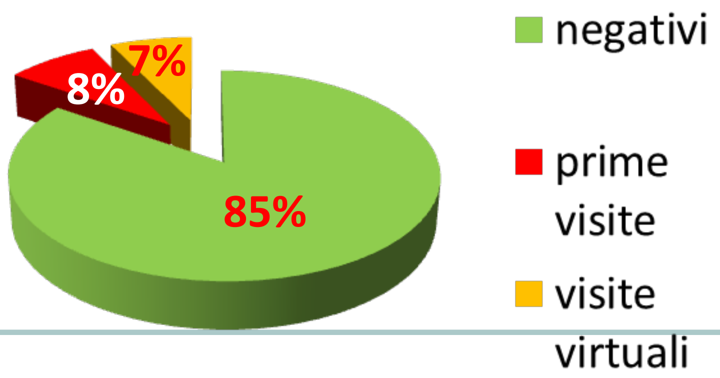
Prestazioni nel 2015: + 35 % rispetto al 2014

Servizio Medico: contatti

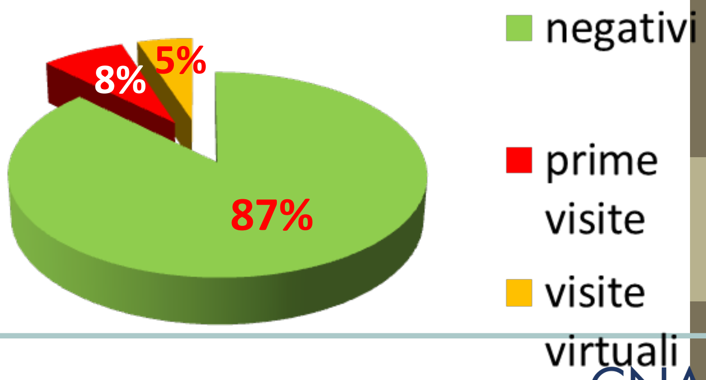




2014



2015 primi 9 mesi



Indicative costs

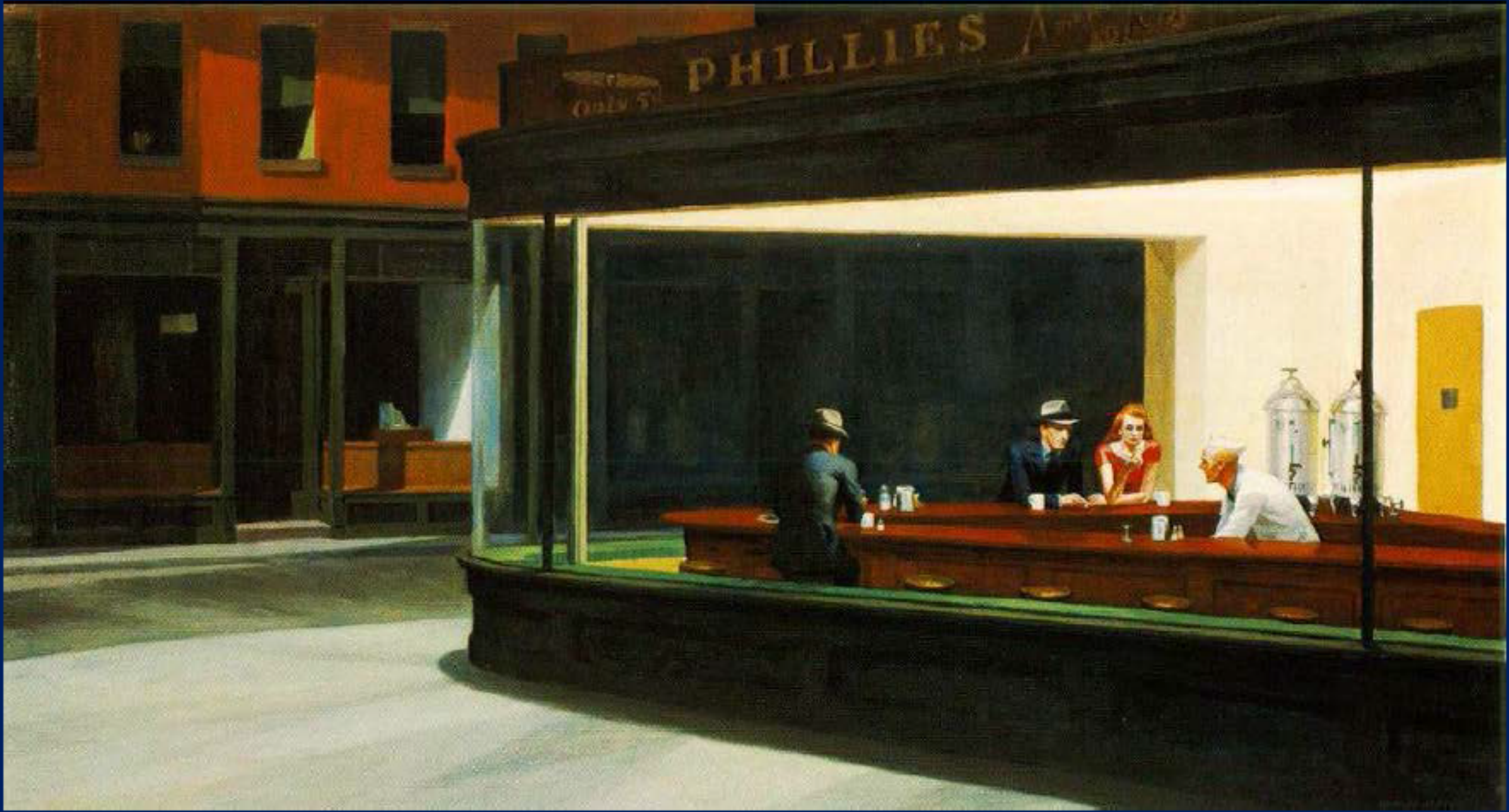
Indicative cost in Italy

- Radiotherapy with X-rays and gamma
  - Normal 2-4- k€
  - Stereotassic 7-8 k€
- Hadron therapy
  - complete cycle 24 k€
- Chemiotherapy
  - Normal: about 2-3 k€
  - Monoclonal: up to 200 k€

Conclusions

- Hadron therapy is a very powerful treatment for cancer
- Three center of excellence in Italy for proton and Carbon beams are currently in function
- Italy offers frontier opportunities in this field

Grazie per l’attenzione



Backup

Neutron Radiotherapy

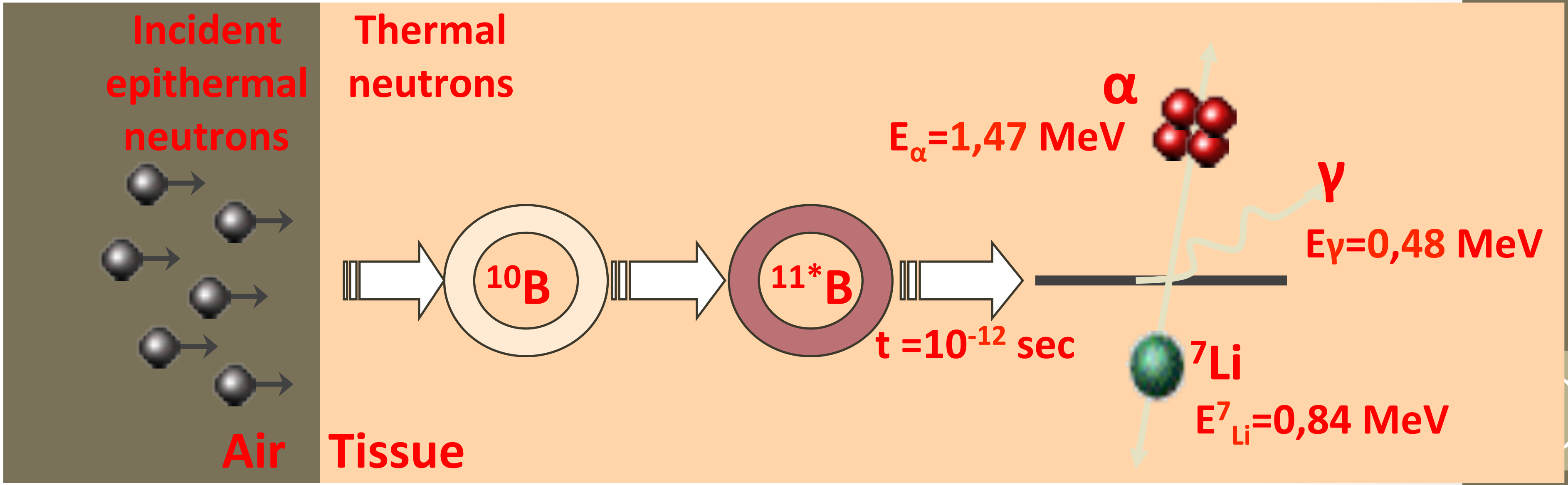
- Boron Neutron Capture Therapy

Boron neutron capture therapy (BNCT)

- Neutron capture therapy might be considered a type of particle therapy, as the damage it does to tumors is mostly from energetic ions produced by the secondary nuclear reaction after the neutrons in the external beam are absorbed into boron-10 (or occasionally some other nuclide), and not due primarily to the neutrons themselves. It is therefore a type of secondary particle therapy.

BNCT-principles

BNCT is a form of cancer therapy which uses a boron-containing compound that preferentially concentrates in tumor sites. The neutrons irradiated interact with the boron in the tumor to cause the boron atom to split into an alpha particle and lithium nucleus. Both of these particles have a very short range (about one cellular diameter) and cause significant damage to the cell in which it is contained.



Incident epithermal neutrons

Thermal neutrons

^{10}B

$^{11*}B$

$t = 10^{-12}$ sec

α

$E_\alpha = 1,47$ MeV

γ

$E\gamma = 0,48$ MeV

^7Li

$E^7{}_{Li} = 0,84$ MeV

Air

Tissue

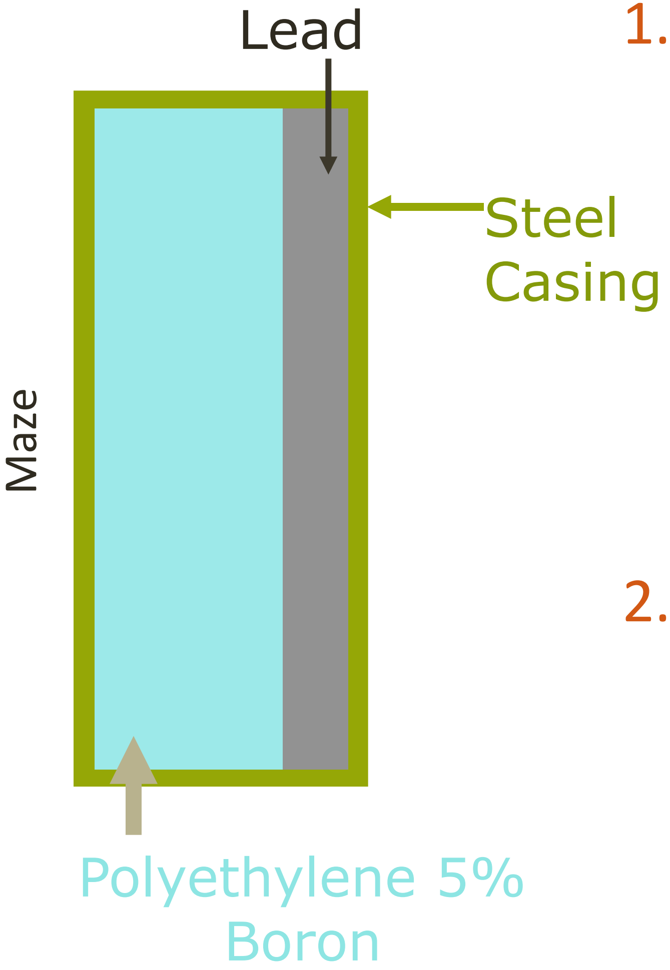
Why Boron

1. it is non-radioactive and readily available, comprising approximately 20% of naturally occurring boron;

2. Emitted particles (α and ^{7}Li) have high LET

3. Chemistry of boron is well understood and allows it to be readily incorporated into a multitude of different chemical structures.

Door Design for Neutron Shielding Details

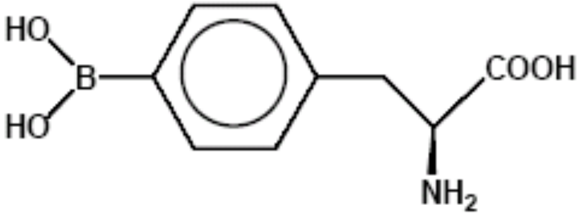


1. Boronated polyethylene:
   - The polyethylene (high H content) slows (moderates) the fast and intermediate energy neutrons to thermal energies.
   - The 5% Boron absorbs the low energy neutrons (high cross section for thermal neutron absorption).

2. Lead absorbs the 0.48 MeV photon that results from the (n,α) and capture gammas (from maze ceiling, and floor).

The boron delivery agent

BPA concentrates in tumor to levels 3.5 - 4 times higher than blood or brain.



L-BPA

(*p*-borono-L-phenylalanine)

12/18/15

^{18}F PET study:
adapted from
Imahori *et al.*
JNM, 39, 325, 1998.

Neutron sources

- **nuclear research reactors**
- **accelerators**
- **radioisotopes (in particular 252Cf)**

Neutron beam requirements

epithermal neutron flux	**≅ 10^9 neutrons/cm^{2}s** **(at the therapy position)**
neutron energy	**~ 1 eV to ~ 10.0 keV**
gamma dose rate	**≤ 2x10-13 Gy/cm^2**
fast neutron dose rate	**≤ 2x10-13 Gy/cm^2**
current:flux (J/Φ) ratio	**> 0.8**

Application

- Brain tumors
- head and neck cancers
- Melanoma
- Colon cancer