



Medical Physics Workshop PET cameras: Principles, use in hospital & ongoing developments

Ohdir, 6-8 September 2015

USE OF PET IN HADRON THERAPY

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USE OF PET IN HADRON THERAPY

✓ PART I: HADRON THERAPY PRINCIPLES

✓ PART II: ON LINE DOSE MONITORING

PART I: HADRON THERAPY PRINCIPLES Outline

- ✓ HISTORY OF HADRON THERAPY
- **✓ PHYSICAL BASICS**
- **✓** BIOLOGICAL BASICS
- **✓ FACILITIES AND TREATMENT TECHNIQUES**
- ✓ CONCLUSIONS AND FUTURE CHALLENGES

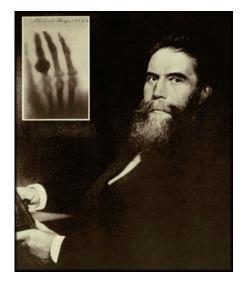
The problem: cancer

Cancer figures among the leading causes of morbidity and mortality worldwide, with approximately 14 million new cases and 8.2 million cancer related deaths in 2012⁽¹⁾.

Available therapeutic strategies

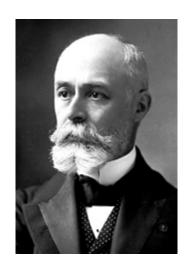
- **surgery**: the most successful therapy for <u>well localized</u> tumors (the earlier the diagnosis and the smaller the tumor, the better the chances for a good therapeutic outcome);
- radiation therapy: used when the tumor is <u>inoperable</u> but is <u>well localized</u> in a specific region of the body (often in combination with surgery);
- **chemotherapy**: used to eliminate the disease when it's <u>spread in</u> the whole body (with distant metastases).

1895: discovery of X rays

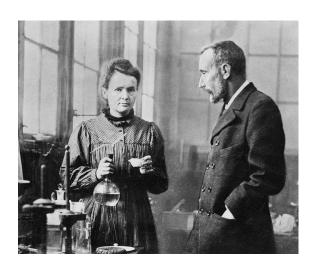


1898: discovery of radioactivity

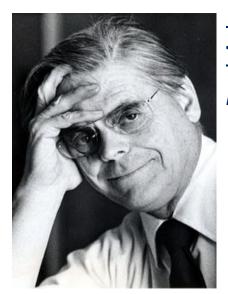




Henri Becquerel



Pierre and Marie Curie



Robert Rathbun Wilson

1946: R. Wilson first proposed a possible therapeutic application of proton and ion beams

R. Wilson, Radiologial use of fast protons, Radiology 47, 487-491, 1946

Radiological Use of Fast Protons

ROBERT R. WILSON

Research Laboratory of Physics, Harvard University Cambridge, Massachusetts

 $\mathbf{E}^{_{_{\mathrm{XCEPT}}}}$ for electrons, the particles which have been accelerated to high energies by machines such as cyclotrons or Van de Graaff generators have not been directly used therapeutically. Rather, the neutrons, gamma rays, or artificial radioactivities produced in various reactions of the primary particles have been applied to medical problems. This has, in irradiate intensely a strictly localized large part, been due to the very short penetration in tissue of protons deuterons

per centimeter of path, or specific ionization, and this varies almost inversely with the energy of the proton. Thus the specific ionization or dose is many times less where the proton enters the tissue at high energy than it is in the last centimeter of the path where the ion is brought to rest.

These properties make it possible to region within the body, with but little skin dose. It will be easy to produce well



1954: first patient treated with deuteron and helium beams at Lawrence Berkeley Laboratory (LBL), California (USA).

The first hadron therapy centers operated at the nuclear and subnuclear physics laboratories:

- 1957: Uppsala (Sweden);
- 1961: Massachusetts General Hospital and Harvard Cyclotron Laboratory (USA);
- 1967: Dubna (Russia);
- 1979: Chiba (Japan);
- 1985: Villigen (Switzerland).

1990: the first hospital-based proton therapy facility at Loma Linda University Medical Center (LLUMC).

LLUMC (California, USA)



Hadron therapy

Treatment of tumors through external irradiation by means of accelerated hadronic particles:

neutrons, **protons**, pions, antiprotons, helium, lithium, boron, **carbon** and oxygen ions.

Protons and **heavy ions** (particles with mass greater than helium) have **physical properties**, and so **radiobiological effects**, such that:

- 1.high and conformal dose is delivered to the tumor target;
- 1.minimazing the irradiation of healthy tissue.

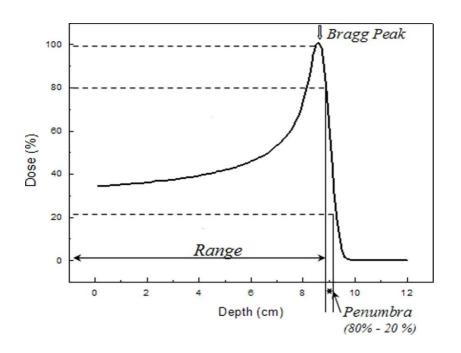
Ideal dose distribution:

- 100% to the target
- 0% to surrounding healthy tissue

Most important physical quantities

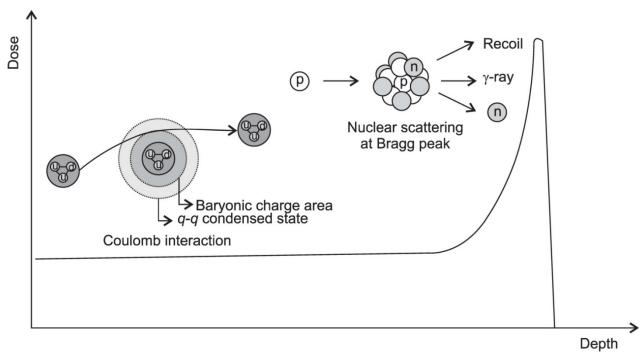
Physical absorbed dose: the mean energy dE deposited by ionizing radiation in a mass element dm

$$Dose = \frac{dE}{dm} [Gy = J/kg]$$



Range: penetration depth such that dose absorbed is 80% of peak value.

Interactions of protons with biological matter



Interactions of protons with biological matter

Seo Hyun Park, Jin Oh Kang, Basis of particle therapy I: physis, Radiat. Onol. J 29(3), 135-146, 2011

Interactions of protons with biological matter

Energy transfer relies mainly on:

- ➤ <u>Coulomb interactions</u> (Stopping) with the <u>outer-shell electrons</u> of the target atoms -> <u>excitation and ionization of atoms</u> -> <u>protons slow down -> energy loss</u> (80 ÷ 90%)
- loss per interaction small -> continuously slow down
- secondary electrons have range < 1mm -> dose absorbed locally

Energy loss is given by **Bethe-Bloch equation**:

$$-\frac{dE}{dx} = Kz^2 \frac{Z}{A} \frac{1}{\beta^2} \left[\frac{1}{2} \ln \frac{2m_e c^2 \beta^2 \gamma^2 T_{\text{max}}}{I^2} - \beta^2 - \frac{\delta(\beta \gamma)}{2} \right]$$

ze Charge of incident particle

Z Atomic number of absorber

A Atomic mass of absorber

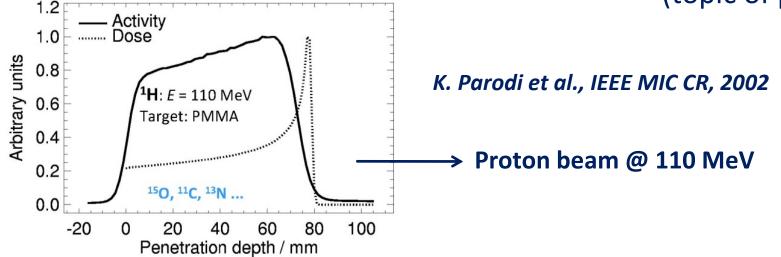
K/A $4\pi N_A r_e^2 m_e c^2/A$

 T_{max} max energy transfer to free electron

I Mean excitation energy

Interactions of protons with biological matter

- ightharpoonup Nuclear reactions: nonelastic nuclear reactions with the target nuclei (energy loss $5 \div 20\%$) -> production of secondaries such as
- protons, α ,recoils nuclei, γ-rays (nuclei excitation),
 neutrons -> radiation safety
- radioactive isotopes (tissue activation), es. ¹⁵O, ¹¹C, ¹³N (β+emitters) -> from isotopes activity 3D dose verification with PET/CT
 (topic of part II)



Interactions of protons with biological matter

Angular deflection of hadrons is due to

➤ Multiple Coulomb Scattering (MCS): elastic Coulomb interactions with the target nuclei -> superposition of small deflections -> beam lateral penumbra (important for its effect on organs at risk)

Proton mass >> electron mass -> deflections for elastic collisions can be neglected

MCS is well described from Moliére theory

$$\theta_0 = \frac{14.1 \text{ MeV}}{pv} z \sqrt{\frac{L}{L_R}} \left[1 + \frac{1}{9} \log_{10} \left(\frac{L}{L_R} \right) \right]$$

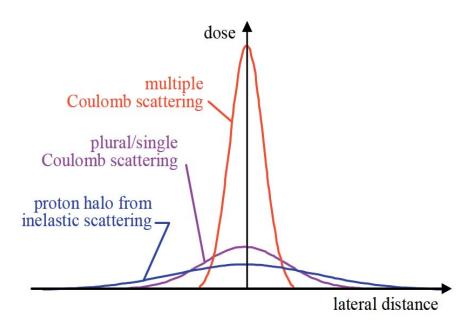
v proton speed

p proton momentum L target thickness

L_R target radiation length

Lateral scattering can be approximately described with a Gauss distribution. 13

PHYSICAL BASICS Interactions of protons with biological matter



Proton beam angular spread caused by MCS, scattering at large angle (very rare) and secondary protons production.

Lateral dose falloff (apparent punumbra) is of great clinical importance because the normal tissues adjacent to the target volume can be exposed to the radiation.

Interactions of carbon ions with biological matter

Due to their heavier mass ions (C-ions) exhibit a <u>sharper lateral</u> dose falloff (small lateral deflection) than protons -> ion beams ideal for the treatment of small target

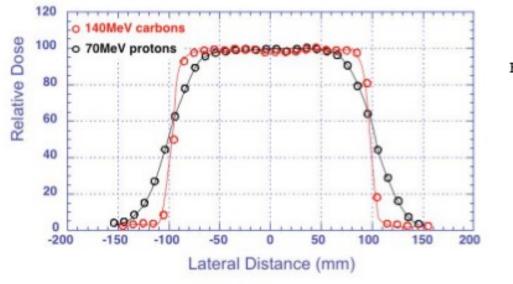


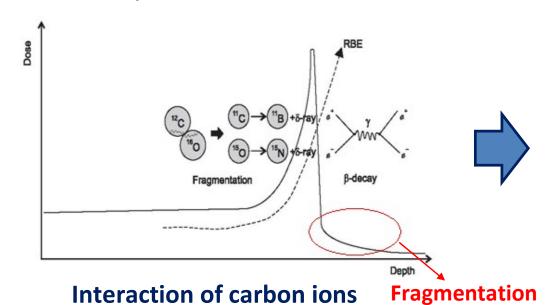
Fig. 4. The penumbra
of a carbon beam is
much sharper than
that of a proton
beam of the
comparable range.
(Based on the paper
presented by H.
Tsuji, at the 39th
meeting of PTCOG,
San Francisco,
October 2002.)

Chu W. T., Columbus-Ohio, ICRU-IAEA meeting, 18-20 March 20006

Fragmentation reactions of heavy ions

At energies of several hundreds MeV/u and at large penetration depths the nuclear reactions may result in a complete disintegration of both projectile and target nuclei (e.g., in central head-on collisions)

tail

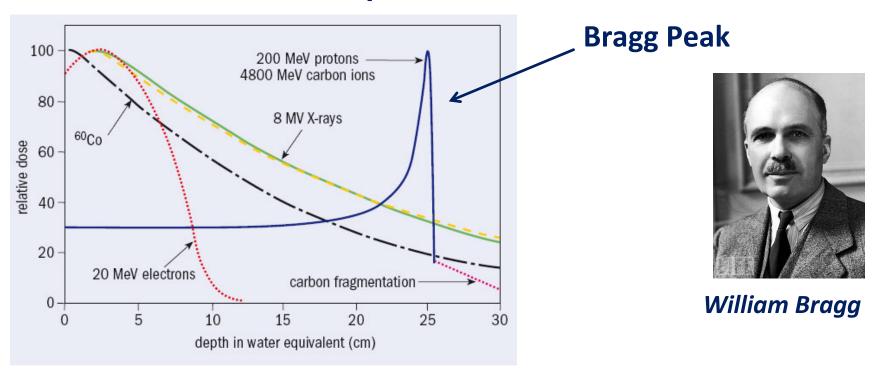


Seo Hyun Park, Jin Oh Kang, Basis of particle therapy I: physis, Radiat. Onol. J 29(3), 135-146, 2011

- ✓ Loss of primary beam particles;
- ✓ the secondary fragments move with about the same velocity as the primary ions and have a longer range -> significant overdose beyond the actual stopping range ->

side effects and secondary cancer inductions. 16

Depth-dose curve



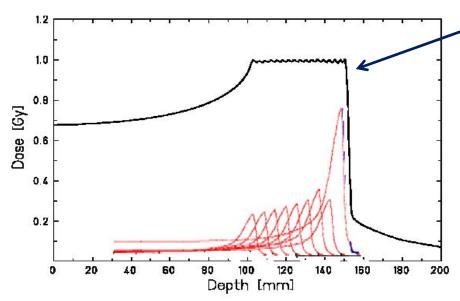
From the **Bethe-Bloch Formula**: $-dE/dx \propto \beta^{-2}$ where $\beta = V/c$

$$-\frac{dE}{dx} \propto V^{-2}$$

the highest dose is released near the end of hadron range giving rise to the "Bragg Peak"

Range and dose distribution calculation must be as accurate as possible

Spread-out of Bragg Peak (SOBP)

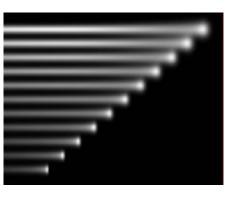


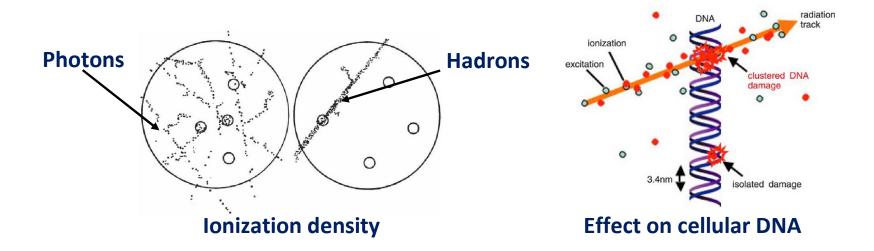
SOBP is the sum of several individual Bragg Peaks at staggered depth.

By modulating the beam energy is possible to cover the whole target volume.



Beam energy modulation



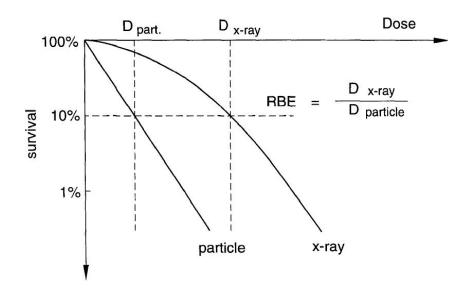


Modern research in particle radiobiology on cellular DNA damage and repair mechanisms now allows an unprecedented insight into the molecular damage induced by fast ions: densely ionising radiation (hadrons) induces a high fraction of clustered DNA damage, which is more difficult to repair and triggers a different intra- and inter-cellular signaling cascade compared to sparsely ionising radiation (X-ray).

Relative Biological Effectiveness (RBE)

RBE: the ratio of the dose of a reference radiation (typically X or γ rays) to the dose of radiation in question to produce an identical biological effect (isoeffect)

$$RBE_{iso} = \frac{D_{X-rays}}{D_{particle}}$$



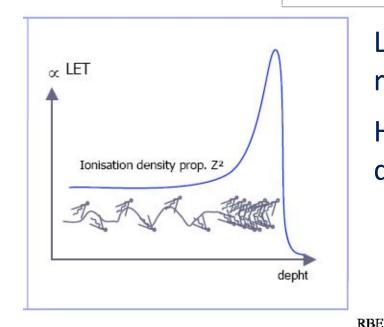
RBE depens on many factors:

- energy;
- particle type;
- organ dimensions;
- tissue type;
- presence of oxygen.

hadrons more biologically effective than photons: lower dose is required to cause the same biological effect

Linear Energy Transfer (LET)

$$LET = \frac{dE}{dI} [keV/\mu m]$$

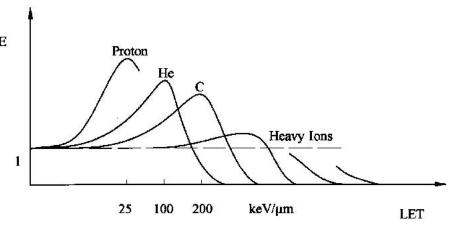


LET -> ionization density -> quality of radiation

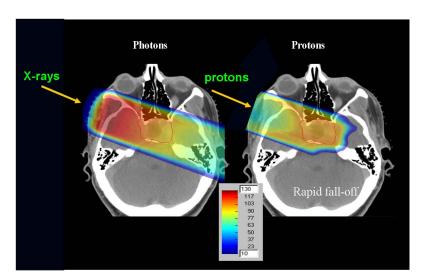
High LET (> 10 keV/ μ m) -> multiple DNA damages

Hadrons are high LET with respect to photons

Relationship between RBE and LET as a function of particle type



Protons Vs Photons



CT image: dose distribution calculated for proton beams and X-rays.

Physical advantages:

- ✓ finite range and high ionization density;
- ✓ lower integral dose;
- ✓ small lateral scattering (larger flexibility).

Clinical advantages:

- ✓ treatment of deep-seated, irregular shaped and radio-resistant tumors;
- ✓ small probability of side effects in normal tissue (critical structrure);
- ✓ proton therapy suitable for pediatric diseases (reduced toxicity).

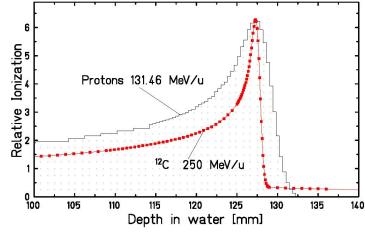
Carbon ions Vs protons

Compared to protons, carbon ions:

- I. allow a <u>more precise concentration of the dose</u> in the target volumes with steeper gradients to the normal tissue;
- II. <u>higher RBE</u> for tumors which are <u>radio-resistent</u> to the conventional treatment.

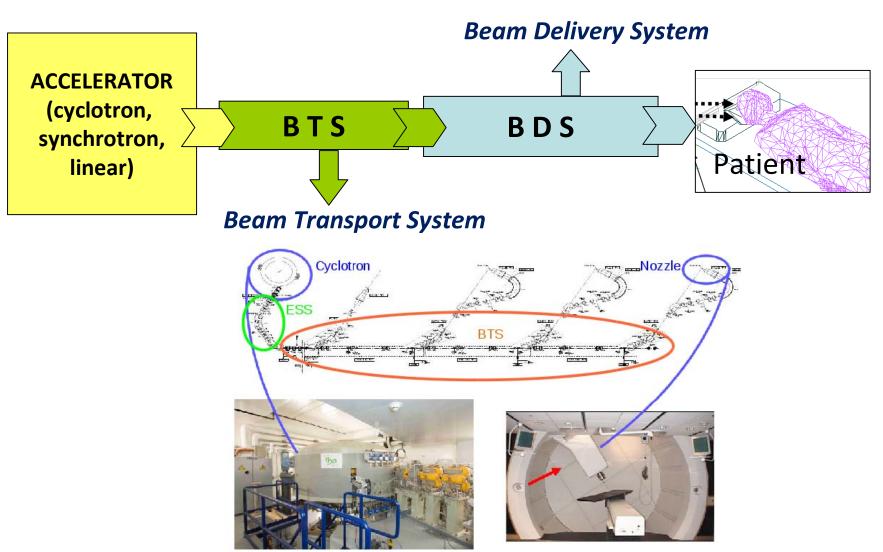
Disadvantage: due to the **nuclear fragmentation**, beyond the Bragg Peak the dose deposition does not decrease to zero -> **overdose**.

Protons are more widely used than carbon ions



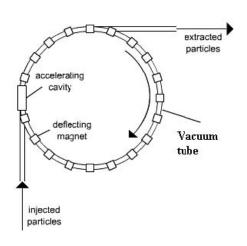
Measured Bragg Peaks of protons and ¹²C ions having the same mean range in water (Schardt et al., 2008).

Main parts of a hadron therapy facility



Hadron therapy facility scheme – IBA (Belgium)

Particle accelerators



Synchrotron: presents a cycle (spill) that lasts about 2 s, beam is present for about 0,5 s and its energy can be varied from spill to spill without passive elements.

Energy range for therapeutic hadron beams:

• p: [60, 250] MeV

• ¹²C: [120, 400] MeV/u

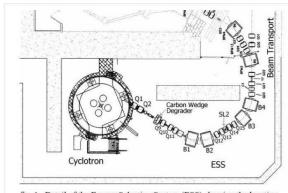
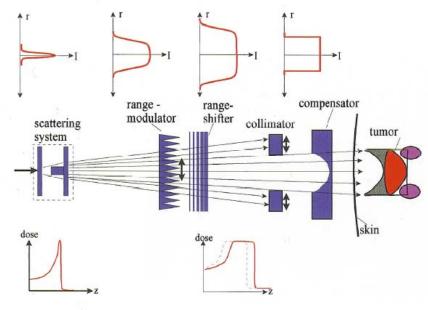


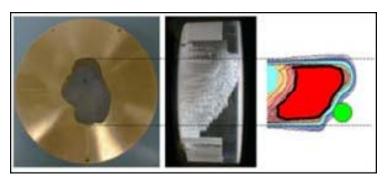
fig. 1. Detail of the Energy Selection System (ESS) showing the location of the carbon energy degrader and the momentum spread limiting slit (SL2).

Cyclotron: high intensity, continuous beam, its energy is fixed and can be degraded with passive absorbers in the Energy Selection System (ESS).

Beam Delivery System – Passive Scattering System



Passive Scattering System



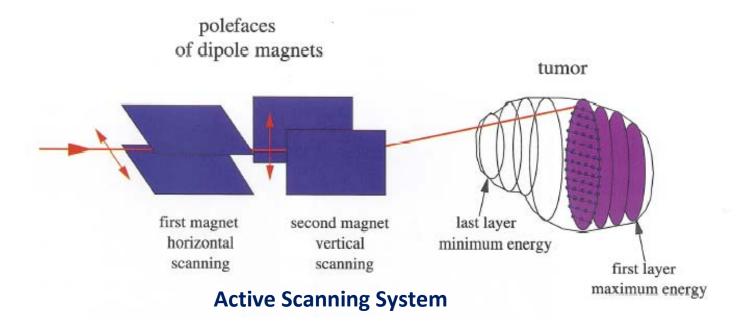
Collimator and compensator

Beam is widened and flattened by means of personalized collimators and compensators. Range shifter (rotating wheel with different thickness) is used to irradiate at different penetration depths (SOBP).



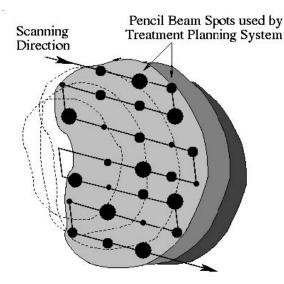
Range Modulator

Beam delivery system – Active Scanning System



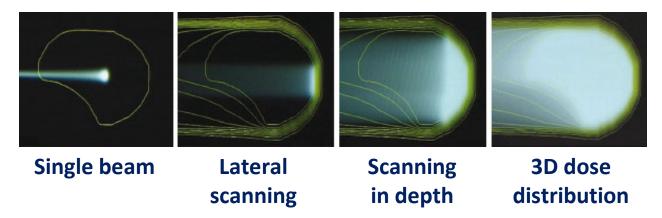
- ✓ Hadrons can be deflected magnetically -> a narrow monoenergetic "pencil beam" can be scanned magnetically across the target volume in a zig-zag pattern in the x-y plane perpendicular to the beam direction (z);
- ✓ the depth scan is done by means of energy variation.

Dose delivery system – Active Scanning System

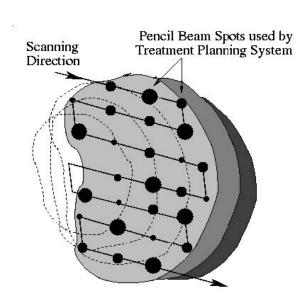


Principle of active beam scanning

Discrete spot scanning: (developed at **PSI** - Zurich) dose is delivered to a given spot at a static position (constant magnet settings). Then the pencil beam is switched off and the magnet settings are changed to target the next spot, dose is delivered to the next spot, and so forth.



Dose delivery system – Active Scanning System



Principle of active beam scanning

Raster scanning: (developed at GSI - Darmstadt) continuous path, beam does not switch off between two voxels (except two spot are away from each other).

Dynamic spot scanning: beam is scanned fully continuously across the target volume. Intensity modulation can be achieved through a modulation of the output of the source, or the speed of the scan, or both.

Active Scanning System vs Passive Scattering System

Advantages of Active Scanning technique:

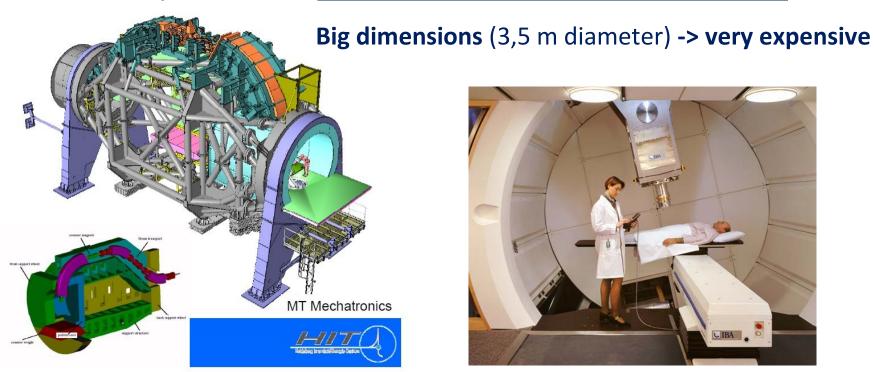
- 1. No need of compensators and collimators (dependent on patient anatomy), the beam has less nuclear interactions outside the patient, this means less neutron contamination and overdose;
- 1. great flexibility, arbitrary shapes can be irradiated with a single beam, this allows **better target conformation**.

Disadvantage of Active Scanning technique:

1. Difficulty to treat "moving organs" (organs subject to motion due to respiration) such as lung cancer, it is necessary to develop systems to synchronize the beam and the patient's respiration.

Gantry and nozzle

Conformal radiation therapy requires target irradiation from any desired angle. The beam is deflected by the magnetic field in the gantry. Treatment nozzle (final part of the gantry) consists of various components for beam shaping and beam monitoring.



Gantry at Hidelberg Ion-beam Therapy Center Treatment room at Boston Northeast (HIT)

Proton Therapy Center (NPTC)

Disadvantage of hadron therapy: the problem of the costeffectiveness

Hadron therapy is useful for treating solid tumors (also combined with standard radiation therapy, surgery and/or chemotherapy) such as:

- 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);
- Noncancerous brain tumors;
- **Pediatric cancers** (only proton therapy for brain, spinal cord and eye tumors);

Disadvantage of hadron therapy: the problem of the costeffectiveness

But <u>hadron therapy is very expensive</u> -> limited availability

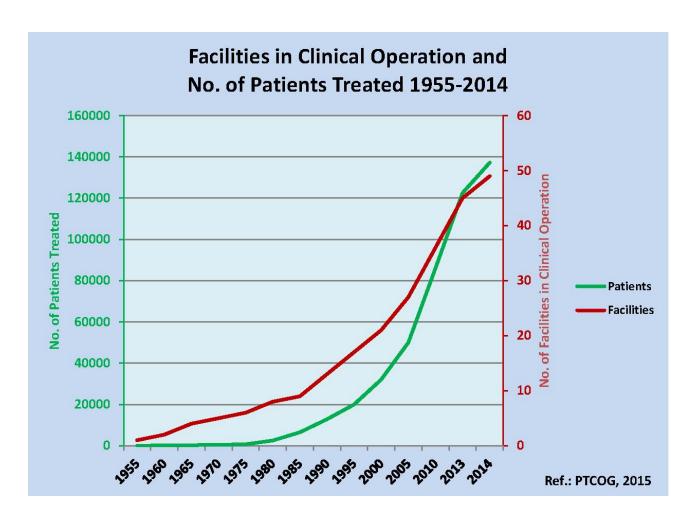
Large investments for building <u>accelerators</u>, <u>beam transport systems and</u> <u>gantries</u>.

The equipmets of a proton thetrapy center is of the order of 100 M€, the operation and tratment/fraction cost must also be considered.

Limited number of clinical studies, so there is an open discussion:

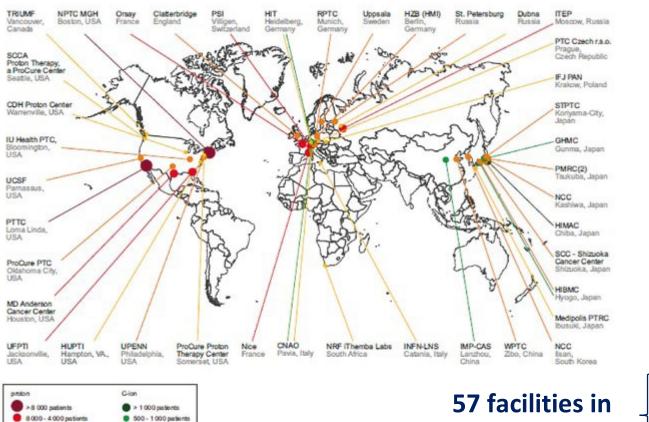
Are the medical benefits large enough to motivate the high costs?

Status of hadron therapy in the world: facilities in operation



From Eugen B. Hug, 2° Annual PTCOG⁽²⁾ 2015 – San Diego.

Status of hadron therapy in the world: facilities in operation



4 000 - 1 000 patients

< 1 000 patients</p>

< < 500 patients

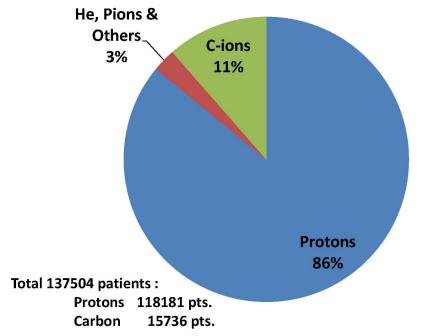
49 with p-beam
4 with C-ion + p beam
4 with C-ion beam

Proton (red-orange) and C-ion (green) centres active worldwide. The size of the spot is proportional to the number of patients treated as indicated in the figure legend.

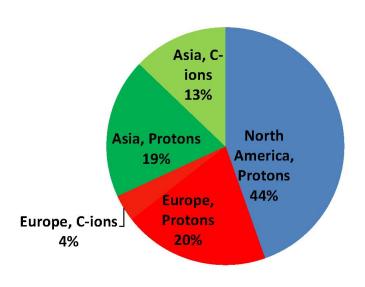
operation⁽²⁾:

Status of hadron therapy in the world: patient statistics





Patients Treated during the year 2014, Protons and C-ions



Total 15432 patients:

Protons 12863 pts. Carbon 2555 pts.

= approx. 80% Protons : 20% Carbon lons

From Eugen B. Hug, 2° Annual PTCOG 2015 – San Diego.

Status of hadron therapy in the world: facilities under construction

Particle therapy facilities under construction:

COUNTRY	WHO, WHERE	PARTICLE(S)	MAX. ENERGY (MeV) Accelerator type	BEAM DIRECTIONS	NO. OF TREATMENT ROOMS	START OF TREATMENT PLANNED	
Austria	Med-AUSTRON	p, C-ion	430/u synchrotron	1 gantry (for protons) 1 horiz fixed beam, 1 fixed beam 0 + 90 dea	3	2016	
China	HITFII, Lanzhou	C-lon	400Au synchrotron	4 horiz, vertical, oblique, fixed beams	4	2015	
China	Rui Jin Hospital, Jiao Tong University, Shanghai	р	250 synchrotron	2 gantries, 1 hortz, fixed beam.		2018?	
France	Centre Antoine Lacassagne, Nice	p	230 S.C synchro- cyclotron	1 gantry		2015	
India	Apollo Hospitals PTC, Chennal	р	230 cyclotron	2 gantries, 1 horiz, fixed beam	3	2018	
Japan	PBTC, Holdkaldo Univ. Hospital, Sapporo	р	220 synchrotron	1 gantry	it	2015	
Japan	Hakuhokai Group Osaka Proton Therapy Clinic Osaka	р	235 synchrotron	1 gantry	1	2016	
Japan	Tsuyama Chuo Hospital PTC, Okayama	P	236 synchrotron	1 gantry	1	2016	
Japan	FROCK, Kanagawa Cancer Center, Yokohama	C-ion	430/u synchrotron	4 horiz., 2 vertical beams	4	2015	20
Netherland	HollandPTC, Delt	p	250 S.C cyclotron	2 gantries, 1 horiz, fixed beam	3	2017	3 U
Netherland	UMC Groningen PTC, Groningen	р	230 cyclotron	2 gantries	2	2017	
Poland	IFJ PAN, Krakow	р	230 cyclotron	1 gantry	1	2015?	
Russia	PMHPTC, Protvino	p	250 synchrotron	1 hortz, fixed beam	ī	20157	ur
Saudi Arabia	King Fahad Medical City PTC, Riyahdt	P	250 SC cyclotron	4 gantries	4	2016	-
Slovak Rep	CMHPTC, Ruzom berok	р	250 synchrotron	1 hortz, fixed beam	1	2015?	CO
South Korea	Samsung Proton Center, Seoul	p	230 cyclotron	2 gantries	2 gantries 2		
South Korea	KIRAMS, Busan	C-lon, p	430/u, 230 synchrotron	2 vertical and horiz, fixed beams, 1 horiz, fixed beam	з	2018	
Sweden	Skandion Clinic, Uppsala	р	230 cyclotron	2 gantries	2	2015	
Taiwan	Chang Gung Memorial Hospital, Talpel	р	235 cyclotron	4 gantries, 1 experimental room	4	2015	
Taiwan	National Taiwan University CC, Taipei	р	250 S.C cyclotron	2 gantries, 1 experim ental room	3	2018	
USA	Robert Wood Johnson, New Brunswick, NJ	P	250 S.C synchro- cyclotron	1 gantry	1	2015	
USA	MD Anderson, Orlando, FL	р	250 S.C synchro- cyclotron	1 gantry	Ť	2015	
USA	Oldahom a University, Oldahom a City, OK	р	250 S.C synchro- cyclotron	1 gantry		2015	
USA	McLaren PTC, Flint, MI	р	250/330 synchrotron	3 gantries	3	2015	
USA	Maryland Proton Treatment Center, Baltimore, MD	р	250 SC cyclotron	3 gantries, 2 hortz, fixed beams	3 gantries, nortz fixed beams 5		
USA	Mayo Clinic Proton Beam Therapy Center, Rochester, MN	р	220 synchrotron	4 gantries	es 4		
USA	Mayo Clinic Proton Beam Therapy Center, Phoenix, AZ	р	220 synchrotron	A gartries 4		2016	
USA	UH Sideman Cancer Center, Case Medical Center, Cleveland, OH	р	250 SC synchro- cyclotron	1 gantry 1		2016	
USA	Emory Proton Therapy Center, , Atlanta, GA	р	250 SC cyclotron	3 gantries, 2 hortz .fixed beams	5	2016	
USA	Texas Center for Proton Therapy, Irvin, TX	р	230 cyclotron	2 gantries, 1 hortz. fixed beam	3	2016	

nder

0 new facilities 26 with p-beam 2 with C-ion + p beam onstruction⁽²⁾: 2 with C-ion beam

Status of hadron therapy in the world: facilities in planning stage

Particle therapy facilities in a planning stage:

COUNTRY	WHO, WHERE	PARTICLE	MAX. ENERGY (MeV)	BEAM DIRECTIONS	NO. OF TREATMENT ROOMS	START OF TREATMENT PLANNED
China	SJFH, Beijing	р	230 cyclotron	1 gantry, 1 horiz fixed beam	2	?
Denmark	DCPT, Aarhus	р	250 SC cyclotron	3 gantries , 1 horiz exp.fixed beam	3	2018
France	ARCHADE, Caen	р	230 cyclotron	1 gantry	1	2018
India	Proton Therapy Hospital, Mumbai	р	open	open	?	2017?
Japan	Teisinaki Corporation, Sapporo, Hokkaido	р	230 cyclotron	1 gantry	1	2018
Netherland	APTC Amsterdam	p	open	2 gantries	2	?
Netherland	PTC, Maastricht	р	230 cyclotron	1 gantry	1	?
Russia	Hospital No.63 PTC, Moscow	р	250 synchrotron	open	?	?
Slovak Rep.	CCSR, Bratislava	р	72 cyclotron	1 horiz fixed beam	1	?
Switzerland	PTC Zürichobersee, Galgenen	р	230 cyclotron	4 gantries , 1 horiz fixed beam	5	?
Taiwan	National Taiwan University CC, Taipei	р	250 SC cyclotron	2 gantries , 1 horiz fixed beam	3	2018
United Kingdom	The Christie Proton Therapy Center, Manchester	р	250 SC cyclotron	3 gantries	3	2018
United Kingdom	PTC UCLH, London	р	250 SC cyclotron	3 gantries	3	2018
USA	Proton Institute of New York, NY	р	230 cyclotron	4? gantries	4?	?
USA	Atlantic Health System , New Jersey, NY	р	330 synchrotron	2? gantries	27	2017?
USA	MGH, Boston, MA	р	330 synchrotron	1 gantry	1	2017?

16 proton beam therapy centers planned⁽²⁾

Hadron therapy facility in Italy

CATANA (Centro di Adroterapia e Applicazioni Nucleari Avanzate)

@ LNS (Laboratori Nazionali del Sud) - Catania

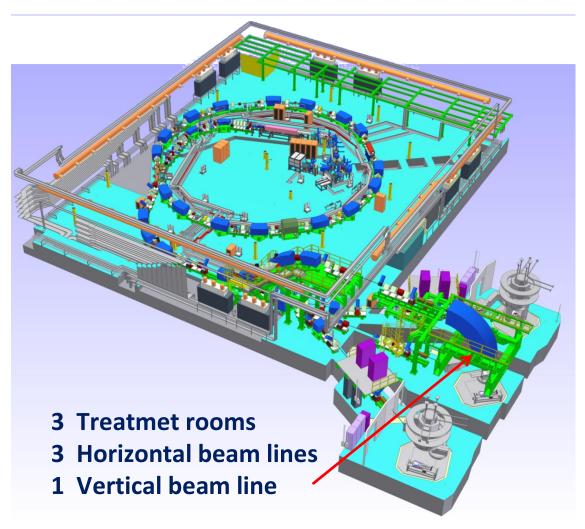


CATANA treatment room

Since 2002 eye tumors are successfully treated with proton beams of 62 MeV produced by a superconducting cyclotron (SC).

Hadron therapy facility in Italy

CNAO (Centro Nazionale di Adroterapia Oncologica) @ Pavia



- Treatments with protons started in september 2011
- Treatments with carbon ions started in november 2012

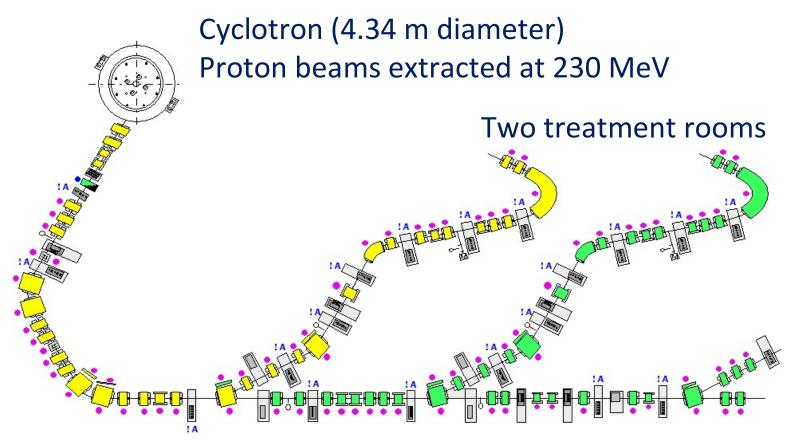
p E: [60, 250] MeV

C⁶⁺ E: [120, 400] MeV/u

Syncrotron (26 m diameter)

Hadron therapy facility in Italy

ATreP (Agenzia Provinciale per la Protonterapia) @ Trento



Inaugurated in July 2013, after commissioning the clinical activity is started last autumn.

CONCLUSIONS AND FUTURE CHALLENGES

Hadron therapy reperesents an important instrument for the cure of cancer;

it can be considered the direct application of high energy physics research and technologies developed for the experiments;

it's a multidisciplinary field (medicine, physics, biology, engineering, IT) in continuous evolution;

there is a great collaboration between research and indutrial partners.

CONCLUSIONS AND FUTURE CHALLENGES

R&D in medical physics and radiobiology is focusing on reducing the costs and increasing the benefits of this treatment

to improve carbon ion treatment and introduce new hadrons (helimun ions) by increasing our understanding of the biological response of cells and tissues (in both tumors and normal organs) to irradiation with various ions;

to improve beam delivery techniques and moving organs treatment;

to construct new and less expensive accelerators (LINAC or laser plasma accelerator).