Overview

• Radiotherapy and Hadrontherapy
• Hadrontherapy facility design criteria
• Layout of a typical carbon synchrotron for hadrontherapy
• Hadrontherapy in the world and future perspectives
Cancer is one of the major world health problems: more than 7 million deaths per year. Radiotherapy is an important technique in the cancer cure: about 40% of cancer patients are cured by radiotherapy, either alone (25%) or in combination with other techniques.
Radiotherapy uses electrons and photons to kill cancer cells damaging the DNA. These particles lose energy at beam entrance and then exponentially. The depth-dose deposition characteristics cause great damage to the healthy tissues too.

Computer-aided treatment plans (IMRT) allows to reduce this counterpart but the problem remains.
Hadrontherapy is the solution!!!!!
It uses hadrons (protons and heavy ions) that have a very localized depth-dose deposition.
Radiotherapy and hadrontherapy

It is possible to localize longitudinally the irradiation only on the tumour target: hadrontherapy is a high precision kind of radiotherapy.
Other figures of Biological merit:

- LET: Linear Energy Transverse
- RBE: Relative Biological Effectiveness
- OER: Oxygen Enhancement Ratio
- Multiple transverse scattering
<table>
<thead>
<tr>
<th>Particle</th>
<th>Cobalt gamma rays</th>
<th>protons</th>
<th>Heavy ions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum LET</td>
<td>10 keV/\mu m</td>
<td>100 keV/\mu m</td>
<td>1000 keV/\mu m</td>
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</tbody>
</table>

**LET** = Linear Energy Transfer

D = distance between ionizations

Low LET: < 20 keV/\mu m
High LET: > 50 keV/\mu m
Very High LET: > 1000 keV/\mu m

D > DNA diameter
D < DNA diameter + excess Energy

300 MeV/u carbon ions

Rayons X
Ions lourds
RBE= the ratio between the photon and the ion doses which are necessary for producing the same biological effect. It gives the efficiency in killing the cells.

Proton RBE = 1.1
Carbon RBE > 3 in the Bragg peak region
>= 1 in the entry channel.

The survival curve for the target cells for late injury is "curvier" than that for acute effects.
## OER and Multiple scattering

<table>
<thead>
<tr>
<th>OER=Oxygen Enhancement Ratio: the dose to produce a biological effect in the absence of oxygen to the dose to produce the same effect in oxygen presence. Photon OER 2.5-3</th>
<th>OER decreases with increasing LET; OER about 1 at LET = 300 keV/µm.</th>
</tr>
</thead>
</table>

When increasing mass the multiple scattering decreases increasing the quality of lateral and longitudinal treatment. However when increasing mass nuclear fragmentation is greater, tailing Bragg peak.

All the biological consideration indicate that heavy ions have more advantages than protons. 
Z>6 heavy ions are not clinically interesting. Carbon ions have indicated in ‘80s as the best medical choice. 
1<Z<=6 heavy ions could be interesting but experimentation is needed and recommended.
The kind of the accelerator depends mainly on:

1. The species to be accelerated

<table>
<thead>
<tr>
<th>particle</th>
<th>Penetration range</th>
<th>Energy range</th>
<th>Brho range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proton</td>
<td>30-300 mm</td>
<td>60-250 MeV/u</td>
<td>1.16-2.31 Tm</td>
</tr>
<tr>
<td>Carbon</td>
<td>30-300 mm</td>
<td>120-400 MeV/u</td>
<td>3.18-6.34 Tm</td>
</tr>
</tbody>
</table>

2. The radiation shaping and delivery method

- Passive Scanning
- Active Scanning
Passive scanning is based on putting several absorbers before the patient to change longitudinal and transverse characteristics.

- Ridge filter
- Bolus
- Multi-leaf final collimator
Active Scanning

Several Bragg peaks from the accelerator paint the tumour longitudinally.

Fast magnets paint the tumour transversally.

A nozzle system controls the dose delivered.

First use in Japan (1980) and then regularly used at GSI, PSI, HIT, CNAO.
Passive system needs patient-specific hardware: Bolus, Multileaf collimator

There are errors on dose irradiation:
• Bolus conforms the most distal surface
• Absorbers > Nuclear Fragmentation > Tailing of Bragg Peak
• Heavy ions need thicker absorbers > greater energy and currents from the accelerator.

Active system needs a more challenging control of beam characterisations and of the scanning magnets but allows a more precise dose irradiation of the tumor target
Active system is critical in the case of moving organs. R&D is in progress worldwide about several techniques: Gating, repainting, beam tracking.

Repainting consists in underdosing the tumour and increasing the treatment sessions.

Gating consists in irradiating only at a specific position of the organ.

Beam Tracking is an adjustment in real-time of treatment plan considering the 4D organ motion signal.
Three accelerators can provide clinical beam: LINAC, Cyclotrons, Synchrotrons. The energy and the species of hadrontherapy make LINAC not very practical and feasible.

Nowadays Hadrontherapy centers are Cyclotrons and Synchrotrons.

<table>
<thead>
<tr>
<th>Cyclotrons</th>
<th>Synchrotrons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compact (4 m diameter)</td>
<td>More complicated</td>
</tr>
<tr>
<td>cheaper</td>
<td>More expensive</td>
</tr>
<tr>
<td>DC beam</td>
<td>Pulsed beam</td>
</tr>
<tr>
<td>High current (hundreds nA)</td>
<td>Smaller current (tens nA)</td>
</tr>
</tbody>
</table>

*BUT...*
Cyclotrons are easy for protons; only a CHALLENGING PROPOSAL exists for carbon.
Cyclotron compactness is partially offset by the place required by the medical structure.
Passive scanning is needed with cyclotrons because the energy from accelerator is fixed.

On the contrary

Synchrotrons can accelerate protons and carbons.
A synchrotron designed for 300mm C6+ can accelerate 1<=Z<=6 and O up to 19 cm.
Synchrotron can perform active scanning.

Nowadays the best technological layout for a hadrontherapy center is a Carbon Synchrotron equipped with active scanning.

A carbon synchrotron facility is made up of:
1. A low energy injector
2. A ring
3. The extraction lines
The injector is placed outside the ring for easier maintenance or inside to save space.
An injector is made up of:
1. Two or three sources
2. A LEBT (Low Energy Beam Transfer line)
3. A low energy Linac
4. A MEBT (Medium Energy Beam Transfer line)
The type of heavy ions sources are PIG, EBIS but, above all, ECR (Electron Cyclotron Resonance)

Gas are ionized by RF power at electron cyclotron resonance frequency (10-18 GHz) The magnetic trap for the electrons is obtained by a solenoid and an expapolar magnet
Permanent magnet (Max 1.2 T)
Double wall, water cooled plasma chamber, 7 mm diameter aperture for beam extraction.

Flexible frequency variable travelling wave tubes amplifiers (TWTA); An RF generator of about 400 W at 14.5 GHz (the effective power used is 8 W for H3+ and 180 W for C4+).

A DC bias system to add electrons to the plasma and decrease the plasma potential.

He, CO2, H2 gas

0.008 MeV/u, ~ 1 mA, 0.67 Pi mm mrad H3+
0.008 MeV/u, ~ 0.25 mA, 0.56 Pi mm mrad C4+

Continuous beam

A electrostatic chopper at the end of the LEBT makes a pulsed beam

A switching magnet in the LEBT allows to select the source and then the species
RFQ + IH

217 MHz

IH

RFQ
0.008-0.4 MeV/u H^3+
0.008-0.4 MeV/u C^4+
IH
0.4-7 MeV/u H^3+
0.4-7 MeV/u C^4+

Four-rod like type
Energy range = 8 – 400 keV/u
Electrode length = 1.35 m,
Electrode voltage = 70 kV
RF power loss (pulse): about 100 kW
Low duty cycle: around 0.1%
Stripping foils

<table>
<thead>
<tr>
<th>Positions:</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foil material:</td>
<td>Carbon</td>
</tr>
<tr>
<td>Foil thickness:</td>
<td>100-200 μg/cm²</td>
</tr>
<tr>
<td>Foil diameter:</td>
<td>15 mm</td>
</tr>
<tr>
<td>Beam diameter:</td>
<td>5 mm</td>
</tr>
<tr>
<td>Position accuracy:</td>
<td>±0,5 mm</td>
</tr>
</tbody>
</table>

\[ H_3^+ \rightarrow H^+ \]
\[ C^{4+} \rightarrow C^{6+} \]

Multiturn injection: a 70 microsec beam injected in a ring with 3 microsec revolution frequency using a variable magnetic bump on the electrostatic septum

CNAO debuncher cavity
Dose homogeneity must be ± 2.5% → a single turn extraction (<1 µsec) not possible

It consists of making unstable beam betatron oscillations: the motion amplitude grows until an electrostatic septum allows the extraction of the particle.

Extraction mechanism strongly influences the ring design

Optical layout must guarantee a machine tune near to an unstable value during the extraction. When extracting beam must acquire the resonance tune.

In the present facilities the unstable tune is chosen N/3. A sextupolar field feeds the resonance:

THIRD ORDER RESONANCE SLOW EXTRACTION MECHANISM
Beam is driven to the resonance condition by three methods:

- **amplitude selection**
- **amplitude-momentum selection**
- **RFKO**
Ring: Slow Extraction

amplitude selection.

amplitude-momentum selection

RFKO

• Not constant optics
• Narrow dp/p
• Not constant position, size, energy of extracted beam
• No more used

• Constant optics
• Large beam dp/p
• Constant position, size, energy of extracted beam
• Use of a betatron core

• Constant optics
• Constant position, size, energy of extracted beam
• Use of a transverse RF exciter
Synchrotron facility layout: Ring

- Broadband RF cavity
- 16 resistive dipoles (1.5 T)
- Electrostatic Septum
- 24 m
- Air core quadrupole
- Betatron Core
Nowadays ferrite often is replaced by amorphous alloy to reduce cavity length.

Acceleration is performed with a single RF cavity at harmonic 1 or 2 based on the principle of ferrite-loaded cavities and with tetrode or solid state technology for the amplifier.

<table>
<thead>
<tr>
<th><strong>Frequency Range</strong></th>
<th>0.4 MHz-3 MHz</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Voltage Range</strong></td>
<td>50 V-10000 V</td>
</tr>
<tr>
<td><strong>Vitrovac current</strong></td>
<td>0-10 A</td>
</tr>
<tr>
<td><strong>Cavity length</strong></td>
<td>1.3 m</td>
</tr>
<tr>
<td><strong>Q</strong></td>
<td>1-5</td>
</tr>
<tr>
<td><strong>Rshunt</strong></td>
<td>900-500 ohm</td>
</tr>
</tbody>
</table>
High inductance device: intrinsically smooth in its operation

The time to cure a voxel is about 5 msec considering the dose homogeneity beam must be controlled in the scale of 10 kHz.

To reduce ripple spill in this range RF cavity is used with the technique of empty bucket channelling.
The beam quality at all the energies (stable position, possibility to have round beams with more dimensions, RT control of the dose) constraints on magnetic lattices, power supplies, magnets, control system, Nozzle.

Irradiation from different directions is mandatory. It can be realized:

1. Displacing the patient
2. Several lines in the same room
3. Gantry

Nowadays gantries for protons are present in most facilities. A gantry for carbon is more challenging! To date only HIT is equipped with a carbon ions gantry (600 tons at 13 m against the standard 100 tons at 10 m)
CNAO Extraction lines

CNAO lines: 3 treatment rooms: 2 with horizontal line and 1 with horizontal and vertical one. The beginning of the line has 4 fast magnets (100 microsec) to dump the beam for patient security.
Radiological Use of Fast Protons

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EXCEPT 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 part, been due to the very short range in tissue of protons, deuterons, and light nuclei from presently available energy machines, i.e., the specific ionization per centimeter of path, or specific ionization per gram, for 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 irradiate intensly a strictly localized region which is invaded by the protons, e.g., a tumor. In this way a very intense dose of radiation is given to tumor cells as they are moving through the region affected by the proton beam. The radiation dose decreases as the tumor cells move away from the region affected by the beam. This makes it possible to achieve a high dose of radiation to tumor cells while giving a low dose to normal tissue surrounding the tumor. This is very important in cancer treatment. The irradiation is very localized, and the dose is very high at the point of entrance of the beam. The dose is lower as the beam travels farther into the tissue. This makes it possible to achieve a very high dose of radiation to tumor cells while giving a low dose to normal tissue surrounding the tumor.

Radiology 47: 487-491, 1946

In 1954: 30 patients treated with protons at LBL (Lawrence Berkeley Laboratory)

In the next years other treatments in other research centers have been performed (Uppsala, Harvard, Dubna, St.Petersburg, Moscow, PSI, Chiba, Tsukuba)

In 1990 the first dedicated hospital facility has started treatments at Loma Linda (LLUMC)
Proton synchrotron (70-250 MeV) equipped with a fixed beam room with two beam lines, three rotating gantries and a research room with three beam lines. To date over 15000 patients have been treated.
Hadrontherapy history: Rapid Growth
Hadrontherapy in the world

Dec 2011: 38 centers
75571 patients of which 7881 with carbon ions
Hadrontherapy in the world: Cyclotrons

UCSF (California), USA
IU Health PTC (Bloomington), USA
NPTC (Boston), USA
UFPTI (Jacksonville), USA
Upenn (Philadelphia), USA
CDH (Warrenville), USA
HUPTI (Hampton), USA
Procure PTC (New Jersey), USA
Procure PTC (Oklahoma), USA

Dubna, Russia
WPTC (Zibo), China
NCC, South Korea

iThemba LABS, South Africa

TRIUMF (Vancouver), Canada

24 cyclotron facilities
Hadrontherapy in the world: Synchrotrons

14 synchrotron facilities
Hadrontherapy in the world: Carbon Synchrotrons

6 carbon synchrotron facilities: only HIT, CNAO and PATRO produce both clinical protons and carbon ions
USA, Europe, Asia: 12 proton cyclotrons; 2 proton-carbon synchrotrons; 2 proton synchrotrons; 1 carbon synchrotron; 1 proton synchro-cyclotron
Hadrontherapy business

The idea of hadrontherapy facilities has passed from the research field to the business field with lots of commercial firms: IBA, Hitachi, Mitsubishi, Sumitomo, Varian, Still River, Optivus, Siemens

• IBA: the greatest number of sold centres: 14 proton resistive cyclotrons. Unique proposal of carbon cyclotron
• Varian (bought ACCEL in 2007): proton superconducting cyclotrons
• Optivus: proton synchrotron similar to LLUMC
• Hitachi: proton synchrotrons similar to LLUMC (4 sold centres)
• Mitsubishi: proton synchrotron (4 sold centres); carbon and proton synchrotron (PATRO)
• Sumitomo: proton cyclotron; carbon synchrotron: injectors installed but not yet full centres
• Siemens: proton-carbon synchrotrons. In July 2011 it communicated its lost of interest: Kiel and Marburg will be dismantled.
• Still River: compact proton superconducting synchrocyclotron (1st under construction, USA)

The field is not only for firms;
Hadrontherapy field is still technologically challenging then research centres still contribute to the design and the construction of facilities: e.g. CNAO was born from the PIMMS and built by the help of a strong net of research international collaborations: INFN-CERN-GSI-LPSC-NIRS-Italian universities (Milan, Pavia, Turin)
Worldwide R&D for more compact and/or advanced accelerators:

- **FFAG**: Fixed Field alternating Gradient: in the middle between a cyclotron and a synchrotron. DC beam with fast energy change! The radius change slightly because B changes with the radius. A fast energy change could be a good solution in treating moving organs.
- **LIBO**: Linac Booster Linac @ 3 GHz, 27MV/m for protons from 30 MeV to 250 MeV exploiting the standard 30 MeV cyclotrons for radioisotopes as injector.
- **Laser**: heavy ions acceleration by high power lasers.
- **DWA**: dielectric wall induction linac: new dielectrics 100 MV/m (instead of 10)

250 MeV proton linac 3 m long
Conclusions

The present clinical results have shown the importance of hadrontherapy and in particular the advantages of the carbon beams over the proton.

The choice of the beam shaping technique is very important. Active scanning appears to be the future but research is mandatory in the case of moving organs.

Synchrotrons designed for carbon beams can easily be adapted also for proton beams.

The more complete centre nowadays is a proton-carbon synchrotron with active scanning.

In the last decades hadrontherapy had a rapid growth with lots of facilities under the form of cyclotrons and synchrotrons for protons and carbon ions.

New centres are under design all around the world.

R&D is mandatory on the clinical characteristics of other species and in the design of more compact and improved layout.