Medical Applications from Physics–2

CERN Summer School Student Lectures, 2018

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Particle therapy: a short history

- Proposed by R.R. Wilson
- 1st patient at Berkeley by Lawrence et al
- 1st patient in Europe at Uppsala
- ITEP, Moscow, Russia
- HIT (carbon), Heidelberg (Germany)
- MedAustron (Austria)
- CNAO, Pavia (Italy)
- Eye tumours, Clatterbridge, UK
- GSI carbon ion pilot, Germany
- CPO (Orsay), CAI (Nice), France
- Loma Linda (clinical setting) USA
- Boston (commercial centre) USA
- NIRS, Chiba (carbon ion) Japan
- PSI, Switzerland
- ENLIGHT
- ENLIGHT 10th year

Timeline:
- 1946
- 1954
- 1957
- 1969
- 1984
- 1989
- 1990
- 1991
- 1992
- 1993
- 1994
- 1996-2000
- 2002
- 2009
- 2011
- 2016
PIMMS at CERN (1996-2000)

400 MeV/u synchrotron

Circumference $C = 76.84$ m
Tune horizontal $Q_x = 1.67$
Tune vertical $Q_z = 1.72$

- Resonance sextupole
- Electrostatic septum

 cà©N-TERA-MedAustron
Facilities in operation then – Europe

Source: PTCOG
Accelerator Technologies

PIMMS 2000 (coordinated by CERN) has led to:

First patient treated with in 2011

From PIMMS study to clinical reality

First patient with carbon ions Nov 2012

Treatment started in 2016
CNAO: Pavia, Italy

Started treating patients in 2011
MedAUSTRON – Wiener Neustadt

Started treating patients in December 2016
[Data from www.ptcog.ch]
Facilities in operation now – Europe (2018)
Centres and patients worldwide

((CC) Manjit Dosanjh)
Much remains to be done ......
Challenge

Smaller, simpler, cheaper
There are now ‘single room’ proton systems

Currently in the market

IBA/SHI – 250 Ton Isochronous Cyclotron

Varian – 90 Ton Isochronous Cyclotron

IBA – 60 Ton Synchrocyclotron

MEVION – 15 Ton Synchrocyclotron
1. Single-room facility by MeVion (the rotating synchrotron was designed by MIT)

9 tesla superconducting synchrocyclotron
2. Single-room facility by IBA: Proteus One

Willis-Knighton Cancer Center in Shreveport, Louisiana
3. Single room facility by Varian (Stanford): ProBeam

superconducting cyclotron
4. Single room facility by SUMITOMO (Japan)

Conventional Gantry

Short-length Gantry

50% DOWN in length

30% DOWN in vault area

360 deg. rotation

360 deg. rotation
Examples of Linacs (‘New kid on the block’)

TOP-IMPLART

RFQ at 750MHz; Accelerating Structures at 3000MHz

Steve Myers, ADAM
RF vs PLASMA ACCELERATORS

Radio-frequency accelerators
- Beam Energy: 6-20 MV
- Energy gain: 10 MV in 1 meter
- Discrete dose range
- 180-360 Hz, <1 mGy/pulse
- Treatment time 5-10 minutes
- Very complex systems
- Old technology, very reliable

Laser-Plasma accelerators
- Beam Energy: up to 300 MV BETTER
- Energy gain: 100 MV in 1 mm
- Continuous dose range
- 50 Hz frequency, 100 mGy/pulse
- Treatment time <1 minute FASTER
- More simple systems
- New technology

Steve Myers, ADAM
However, no similar solution exists for heavier ions
Recent workshop: beyonds PIMMS

Take away words:
- Small and cheap
- Fast delivery
- Real time imaging
- Low consumption
- Higher intensity
- Possibly with MRI
- “Start from the patient”

Two technical options

Superconducting synchrotron
Four 90deg canted cosine theta magnets, Bmax 3.5T, ring 27m, gantry r=5.3m

Linear accelerator
Folded linac, 34m length, high rep. frequency and intensity, low emittance

Both options require development!

SC synchrotron compared to CNAO and Medaustron
Plan of Miniaturizing Machine

1st Model: HIMAC
2nd Model: GHMC
3rd Model
4th Model: Next Generation
5th Model: Future Type

Future Plan

Courtesy of Dr. Kojii Noda
Challenge

More compact, cheaper, energy efficient
Superconducting rotating-gantry
(constructed in 2015)

Use of superconducting (SC) magnets

- Ion kind: $^{12}\text{C}$
- Irradiation method: 3D Scanning
- Beam energy: 430 MeV/n
- Maximum range: 30 cm in water
- Beam orbit radius: 5.45 m
- Length: 13 m

The size and weight are considerably reduced

Weight: order of 300 tons

Iwata, NIRS group
A compact facility for CIRT is being constructed at Yamagata University.

2nd-generation compact gantry will be installed.
Challenge precision
Challenges for Particle Therapy

• The good thing: Particles stop
  The bad thing: We do not know where exactly

• Range uncertainty: 3.5 % + 2 mm

![Diagram showing range uncertainty with +7 mm and +9 mm tolerances.]
The Bragg Peak

• Allows more precise allocation of the dose to the tumour
• BUT makes dosimetry and diagnostics more difficult because the energy is deposited preferentially inside the patient
• To take full advantage, we need improved diagnostics
  • To steer the beam spot by measurement of the location of the energy deposition
  • To control the dose (dosimetry)
Challenge

Safer and more effective therapy: moving organs
Treating moving targets

- **Motion**: Geometric miss of target
- **Range changes**: Position of Bragg Peak under motion
- **Interplay**: Interference between scanning and tumor motion
- **Current solution**: ITV, rescanning
- **Future**: 4DTP, online tracking

Courtesy of Christian Graeff, GSI, Germany
Challenge

Clinical trials: protons, carbon, ions, multi-centric
RBE – the weakest link

Must be clarified to secure optimal particle therapy

Jens Overgaard, Divonne Brainstorming, 2016
Two sides of Radiation

Icon made by Freepik from www.flaticon.com
The Beginning ..............

X-rays
- November 1895:
- 1901: first physics Nobel prize

Wilhelm Röntgen
Henri Becquerel
(1852-1908)

1896: Discovery of natural radioactivity

1898: Discovery of radium
used immediately for “Brachytherapy”

Thesis of Mme. Curie – 1904
$\alpha$, $\beta$, $\gamma$ in magnetic field

Marie Curie  Pierre Curie
(1867 – 1934)  (1859 – 1906)
First radiobiology experiment: Pierre Curie

The first radiobiology experiment. Pierre Curie using a radium tube to produce radiation ulcer on his arm. Hall fig. 1-2
Early results.....

1896 – First radiation therapy of a cancer patient (Victor DESPEIGNES, Lyon)
1896 - First diagnostic use Kaiser, Vienna
1899 - The first successful radiation treatment of tumour - Thor Stenbeck, Stockholm
1900 – Palliation of tumour
1902 - Radium used to treat pharyngeal carcinoma in Vienna
1904 - Patients in New York undergoing implantation of radium tubes in the tumours
1904 - Chromosomal damage caused by radiation in embryos
1907 - The first described fatal cases (11) of cancer
1910 - Hypothesis - Cancer arises from damage on the chromosomes (Muller)
1911 - The first specification of skin cancer (94 cases) - Herman Hesse
1911 - Report on radiation causes mutation in fruit fly Drosophila - Herman Muller
1917 – Observations of sterility among radiologists
1921 – The 100\textsuperscript{th} death among radiologists
1926 - Muller showed radiation’s role in mutation and that chromosomes are target
Radiation Dose

- Radiation effects depend on DOSE = Energy Deposited by Radiation per Unit Target Mass
- Dose is measured in Gray (Gy) (=1 joule / kg)
- ..but different radiations have different effectiveness (Q)
- Equivalent dose = QxD is measured in Sievert (Sv)
- For X-, γ-rays and electrons: 1 Gy = 1 Sv
- But, for example: 1 Gy α-particles = 20 Sv (Q=20)

- Mammography = 0.01 mSv
- Average background radiation dose on Earth = 3 mSv/year
- Occupational limit = 50 mSv/year
- Lethal dose = 4.5 Sv
- Radiotherapy = 60-70 Gy (to the tumour)
- Average background radiation dose in space = 1 mSv/day
## Radiation Sickness

<table>
<thead>
<tr>
<th>System effected/ Syndrome</th>
<th>Symptoms</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nervous system</strong></td>
<td></td>
<td>100 Gy</td>
</tr>
<tr>
<td>CNS or Cerebrovascular Syndrome</td>
<td>Shock, severe nausea, disorientation, seizures, coma</td>
<td></td>
</tr>
<tr>
<td><strong>G.I. system</strong></td>
<td></td>
<td>10 Gy</td>
</tr>
<tr>
<td>Gastrointestinal Syndrome</td>
<td>Nausea, vomiting, diarrhea, dehydration</td>
<td></td>
</tr>
<tr>
<td><strong>Blood cells / bone marrow</strong></td>
<td></td>
<td>3-8 Gy</td>
</tr>
<tr>
<td>Hematopoietic Syndrome</td>
<td>Chills, fatigue, hemorrhage, ulceration, infections, anemia</td>
<td></td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td></td>
<td>10 Gy</td>
</tr>
<tr>
<td>Erethema</td>
<td>Burning/ infection, sloughing of skin, hair loss</td>
<td></td>
</tr>
<tr>
<td><strong>Ovaries/Testes</strong></td>
<td>Sterility</td>
<td>0.6-0.8 Gy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2-6 Gy</td>
</tr>
</tbody>
</table>
Variation in Radiation Sensitivity Among Adult Human Organs

Approximate Tolerance Dose (TD) beyond which there is a high probability of delayed injury, e.g. 5% clinical injury within 5 years after exposure.
Typical doses in mSv

- Dental X-ray
- Chest X-ray
- Breast X-ray
- Spine X-ray
- Natural radiation per year
- CT Scan - Head

- Airline crew flying polar route (annual)
- Dose in full-body CT scan
- PET
- CT Scan - abdomen and pelvis
- CT Scan - heart
- PET+CT
- Curative RT
- 5 year maximum limit rad. Workers
- Lowest annual dose increase cancer
Questions

- What is radiobiology?
- Why do we need biology for radiotherapy?
- What kinds of biology are important for radiotherapy?
- How do you investigate biological effects of particle beams?
- What do the data tell you?
- Do we know everything we need to know?
Role of radiobiology in radiotherapy?

• plays an important role in providing safe and effective application of radiation in cancer treatment both imaging and treatment

• provides a rationale for implementation of treatment strategies, especially new treatment strategies

• Treatment outcome depends on:
  – clinical situation (extent of cancer, type of tumour, node, metastasis)
  – total dose delivered
  – fractionation scheme
    • Dose per fraction
    • Intensity of dose delivery
    • Treatment time
Cell survival curves

- describe the relationship between the radiation dose and the proportion of cells that survive
- presented with the dose plotted on a linear scale and the surviving fraction on a logarithmic scale

1956: The first in vitro radiation survival curve on mammalian cells by Puck & Marcus
Cellular Survival Curves and Relative Biological Effectiveness

\[ \frac{D_x}{D_i} = \text{RBE} \]
RBE and how does it vary

- Varies with type of radiation
- Varies with type of cell/tissue
- Varies with the biological effect under investigation
- Varies with dose rate and fractionation
- An increase in RBE in itself does not offer therapeutic advantage unless there is differential effect between normal and tumour tissues
- OER (oxygen enrichment ratio) affects RBE
- Effected by presence of other chemicals present
Cell killing by different radiation types

Figure 3.1. Colonies obtained with Chinese hamster cells cultured in vitro. A: In this unirradiated control dish 100 cells were seeded and allowed to grow for 7 days before being stained. There are 70 colonies; therefore the plating efficiency is 70/100, or 70%. B: Two thousand cells were seeded and then exposed to 800 rad (8 Gy) of x-rays. There are 32 colonies on the dish. Thus:

Surviving fraction = Colonies counted / (Colonies seeded x 100)

= 32/2000 x 0.7

= 0.0123
Chromatin Rejoining From Heavier Ion Damage is Slower.

Graph showing the unjoined chromatin breaks (%) over time for different ions:
- Neon (183 keV/µm)
- Argon (115 keV/µm)
- Carbon (13.7 keV/µm)
- Proton (0.562 keV/µm)

The graph illustrates that the rate of chromatin rejoining is slower for heavier ions, with neon showing the slowest rejoining rate compared to the lighter ions.
DNA damage
Single strand break
DNA double break triggers cell death
How does it work?

Radiation damages DNA in all cells and healthy cells get damaged too.

Advantages of hadrons is that they stop in localised position and specially larger hadrons such as carbon cause more complex and lethal forms of damage.
Track Structures of Proton vs. Carbon Ions

Linear Energy Transfer (LET) stands for the radiation energy deposited per unit length in tissue.

- X-rays and proton beams are low-LET radiations
- Heavy ion beams are high-LET radiation in Bragg peaks

Biological advantages:
- High LET to provide significant differences in DNA damages
- Suppression of radiation repair
- Yet avoids some complications with higher-Z ions
Hey, I’ve solved your clinical problem

I didn’t know I had a problem

Physicist

Physician

Courtesy D. Townsend
Collaboration is key

- Imaging centres
- Biologists
- Research institutes
- ICT
- Academic institutes
- Policy makers
- Doctors
- Funding agencies
- Industry
- Hospitals
- Epidemiologists
- Physicists & Medical physicists
European Network for Light Ion Hadron Therapy

- Create common **multidisciplinary platform**
- Cancer treatment
- Identify **challenges**
- Share **knowledge**
- Share best practices
- Harmonise data
- Provide **training**, education
- Innovate to improve
- Lobbying for funding

Leveraging Physics collaboration philosophy into a multidisciplinary medical environment

[www.cern.ch/enlight](http://www.cern.ch/enlight)
New Advances are on their way

The tumour and only the tumour…..
The next challenge: PET + MRI

Detectors in magnetic field
Concept of MRI guided accelerator

- Accelerator
- MLC
- Beam

Seeing what you treat at the moment of treatment

Bringing certainty in the actual treatment

Bas Raaymakers, Utrecht, UMC, ENLIGHT
Utrecht solution: Integrating a Philips MRI scanner with a Elekta radiotherapy accelerator

1.5T 70 cm bore Philips Ingenia

Lagendijk and Bakker, MRI guided radiotherapy - A MRI based linear accelerator
Radiotherapy and Oncology Volume 56, Supplement 1, September 2000, 220
Real-time monitoring

- In-beam PET @ GSI (Germany)
- MonteCarlo simulations
- Organ motion
Prompt gamma Imaging Camera

- Prompt gammas: Resulting from nuclear interactions of beam particles with tissue $^{12}\text{C}$

  - Prompt gammas: Resulting from nuclear interactions of beam particles with tissue $^{12}\text{C}$
  - Prompt gammas: Resulting from nuclear interactions of beam particles with tissue $^{12}\text{C}$

- Emitted directly after the interaction (prompt)
- Energy spectrum: $E \leq 8\text{ MeV}$
- Strong spatial correlation of gamma emissions with dose deposition
The InSide Project

DOSE PROFILER
Prompt secondary particles imaging

BI-MODAL IMAGING SYSTEM
for particle range monitoring and verification

IN-BEAM PET
induced $\beta^+$ activity imaging
Delivery of particles to patient

- **Passive scattering**: scattering through a material to spread the beam over tumor (until a few years ago: the only method used)
  - High dose delivered outside target
  - Individual scattering device for each patient
  - Neutron background
  - “Old technology” (...but still in use in many centers!)

*Figure-2a. Diagrammatic representation of a typical passive scattering proton beam delivery system.*
Spot Scanning

Second delivery technique:

**Spot scanning**: beam is steered with magnets towards the target position

+ More conformal dose
+ No individual hardware
+ Less neutrons
+ Modern state-of-the-art technique

Strong points of LIGHT system:
- XY position accuracy < 0.5 mm
- We can change energy, position and intensity of every pulse

**Spot scanning is chosen for LIGHT**
Active “raster scanning” technique by GSI with respiratory gating (PSI)

The synchrotron beam is moved continuously.
Theragonistics: Terbium Swiss Army Knife

$^{149}$Tb-therapy

$^{152}$Tb-PET

$^{161}$Tb-therapy & SPECT

$^{155}$Tb-SPECT

Müller et al., JNM 2012
$^{149}$Tb: Useful for $\alpha$-Therapy and PET Imaging

PET/CT scan of a AR42J tumor-bearing mouse performed 2 h after injection of $^{149}$Tb-DOTANOC

N. van der Meulen et al., PSI, ICTR-PHE2016.
The Archamps Workshop

“Ideas and technologies for a next generation facility for medical research and therapy with ions”, ESI Archamps (France, Geneva area), June 19-21.

Co-organized by CERN, ESI, GSI - 63 participants

Objectives:

1. Highlight the potential of ion therapy for cancer.
2. Share the current experience: advantages and disadvantages of present implementations, ideas for future facilities, directions for improvement.
3. Explore the options for the design for a next generation medical research and therapy facility with ions in Europe, identify and motivate a community that could contribute.
4. Identify basic parameters, a set of technical options, and outline a possible basic R&D programme.
Recent workshop: beyonds PIMMS

Take away words:
- Small and cheap
- Fast delivery
- Real time imaging
- Low consumption
- Higher intensity
- Possibly with MRI
- “Start from the patient”

Two technical options

Superconducting synchrotron
Four 90deg canted cosine theta magnets, Bmax 3.5T, ring 27m, gantry r=5.3m

Linear accelerator
Folded linac, 34m length, high rep. frequency and intensity, low emittance

Both options require development!

SC synchrotron compared to CNAO and Medaustron
Current Challenge: how to go from no radiotherapy to high quality radiotherapy globally: Challenging Environments
World wide radiotherapy coverage
Availability of RADIATION THERAPY

Number of Radiotherapy Machines per Million People

2012

Source: DIRAC (Directory of Radiotherapy Centres), 2012 / IAEA

For more information: http://www-naweb.iaea.org/nahu/dirac/dirac@iaea.org

Manjit Dosanjh, HST 2018
Globally 15 million cases in 2015 to 25 million in 2035:

• 12,600 megavolt-class treatment machines
• 30,000 radiation oncologists
• 22,000 medical physicists
• 80,000 radiation technologists

Massive challenge need a sustainable solution for both near-term and long-term (which covers Linacs, trained personnel and infrastructure).

Aiming for near-term and long-term solution
Reality in numbers......

• No radiotherapy in 36 countries
• HIC have over 60% of all teletherapy machines and 16% of the world population
• LIC and LMIC have less than 10% of teletherapy machines which serve 50% of the world

Manjit Dosanjh, HST 2018
Desirable features regarding LINACs designed for LICs (I)
Pomper MA et al. The Stanley Foundation

• To be able to function despite:
  – regular interruptions to the power supply,
  – lack of air temperature control in buildings.

• Environmentally friendly radiotherapy accelerator that:
  – consumes little power on standby, and has low instantaneous power demand,
  – has reduced heat production.

• Other desirable features of such LINACs:
  – to be highly modular, so that parts can be easily exchanged,
  – to be self-diagnosing if the machine becomes non-functional.

David Jaffray, ICARO 2017
Desirable features regarding LINACs designed for LICs (II)
(Pomper MA et al. The Stanley Foundation, CNS, 2016)

- A developing-world LINAC with modular enhancements, as capability increases: an option for LINAC companies to consider.

- Costs could be phased in by starting with a basic unit, and options could be provided for:
  - new technology,
  - remote diagnosis and adjustment,
  - Lego-like structure
RADIOThERAPY IN AFRICA

21 countries with RT in 1995

23 countries with RT in 2017

60 YEARS OF MEGAVOLTAGE RADIOThERAPY IN AFRICA

Historical mean = 0.1 MV unit per million population

Manjit Dosanjh, HST 2018
RADIOThERAPy IN AFRIcA

21 countries with RT in 1995

23 countries with RT in 2017

60 YEARS OF MEGAVOLTAGE RADIOThERAPy IN AFRIcA

Historical mean = 0.1 MV unit per million population

0.25 MV units per million population (1 MV unit serves 4 million), in contrast with HIC with 5 MV units per million (2000% difference)

Manjit Dosanjh, HST 2018
Many thanks to:

- U. Amaldi, CERN & TERA
- E. Blakely, LBNL, USA
- M. Durante, GSI, Germany
- HIT, CNAO, MedAustro, PSI and ENLIGHT colleagues
- MARS BioImaging Ltd

Useful links

- cern.ch/crystalclear
- cern.ch/enlight
- cern.ch/virtual-hadron-therapy-centre
- http://cds.cern.ch/record/1611721
- cern.ch/knowledgetransfer
- cern.ch/medipix
- cern.ch/twiki/bin/view/AXIALPET
- cern.ch/medaustron
- cern.ch/fluka/heart/rh.html
- www.fluka.org/fluka.php
- cern.ch/wwwwasd/geant
- cern.ch/wwwwasd/geant/tutorial/tutstart.html