APPLICATIONS OF ACCELERATORS
TO TUMOUR THERAPY - 1

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University of Milano Bicocca and TERA Foundation
The beginnings: neutron beams
1935: Ernest Lawrence persuaded his brother, John Lawrence, to come to Berkeley and apply physics to treat cancer.

Ernest and John at the control of the 37-inch cyclotron used to produce
- radioisotopes
- neutron beams
Robert Stone and John Lawrence treat a patient with neutrons from the 60-inch cyclotron.

deuterium + beryllium $\rightarrow$ fast neutrons

1948: R. Stone evaluated the effects on
24 pts treated at the 37-inch and 226 treated at the 60-inch cyclotrons

“Neutron therapy as administered by us has resulted in such bad late sequelae in proportion to the few good results that it should not be continued.”
Neutron therapy starts again

1965 - Mary Catterall at the Hammersmith Hospital:
- better beam and more fractions
- good results for superficial adenocarcinomas

1978 - Bob Wilson and Chicago oncologist
- 60 MeV Fermilab linac for ‘Neutron Therapy Facility’

Present: 20 000 patients treated
- 5 facilities mainly for salivary gland tumours

National accelerator Centre (Faure – South Africa)
- 66 MeV p+Be
Protontherapy
The first steps at the Berkeley laboratory

In 1946 Robert Rathbun Wilson (*):

- 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
- Carbon ions can also be effectively used

The 184-inch cyclotron - 1946

Cornelius Tobias
1918-2000

At the Berkeley Laboratory
First treatment of pituitary glands: 1954
Treatment of pituitary tumors: 1956
1000 patients by the end of the program 1974

“Irradiation Hypophysectomy and Related Studies Using 340-MeV Protons and 190-MeV Deuterons”
Börje Larsson


(1931-1998)
During World War II the Harvard cyclotron was moved to Los Alamos.

In 1943, the Manhattan project needed the Harvard cyclotron for nuclear studies. Radiologist Dr. Hymer Friedell came to Harvard with a "cover story" that it was needed to make isotopes for Army hospitals. The photograph shows Hymer Friedell (left) discussing with the department chairman Percy Bridgeman (right). Robert Wilson (middle) reported years later Percy Bridgeman's response:

"If you want it for what you say you want it for, you can't have it. If you want it for what I think you want it for, of course you can have it."

After the war Bob’ Wilson is hired as an associate professor at Harvard and designs a new 160 MeV cyclotron.
The new Harvard cyclotron in 1949

Completed 1949

Max. energy = 160 MeV
Avg. power = 250 KW
COST = 0.75 Million (1948$)

(L) Dr. Lee Davenport  (R) Dr. Norman Ramsey
June 10 1949
Andy Koelher was ‘the physicist’ at the Harvard cyclotron.

2002

1953
The three programs at the Harvard cyclotron (9116 pts)

Neurosurgery for intracranial lesions
(AVMs)
(3,687 patients)
Neurosurgery Dept. of MGH
Raymond N. Kjilberg, Bernard Kliman

Eye tumors
(2,979 patients)
Massachusetts Eye and Ear Hospital.
Ian Constable, Evangelos Gragoudas

Larger tumors
(2,449 patients)
Radiation Medicine Dept of MGH
Herman Suit, Michael Goitein,
Joel Tepper, Lynn Verhey
First important results obtained at MGH-Harvard

Condrosarcomas, protons

Cordomas, protons

conventional RT

Control (%)

100%

98%

70%

<35%

5 years

10 years

15 years
30 years of pioneering protontherapy in physics labs

- Lawrence Berkeley Laboratory, USA, 1954
- Uppsala, Sweden, 1957
- Harvard Cyclotron Laboratory (*), USA, 1961
- Dubna, Russia, 1964
- Moscow, Russia, 1969
- St. Petersburg, Russia, 1975
- Chiba, Japan, 1979
- Tsukuba, Japan, 1983
- Paul Scherrer Institute, Switzerland, 1984

(*): 9,115 patients were treated with protons before the laboratory closed in 2002
University of Tsukuba and KEK facility

1983 - 2000: 700 patients treated at the KEK synchrotron

2000 - 2007: 1046 patients treated at PMRC, close to University Hospital
First hospital centre: Loma Linda University Medical Center

- Dr. James Slater MD
- 2007: 180 sessions/day

First patient: 1990
Light ion therapy
Clinical treatments end with the closure of the Bevatron cyclotron.

More than 2,500 patients have been treated since 1954.
New techniques of light ions at Berkeley

First “Raster scanning”

‘Bill’ Chu
"Tobias and collaborators studied

- carbon,
- oxygen,
- neon (400 patients)

beams revealing both physical and biological characteristics favourable to eradicating hypoxic, radioresistant tumour cells at deep locations in the body, while sparing radiation damage to overlying normal tissues"

Eleanor Blakeley, Lawrence Radiation Laboratory

Later it was found that the neon ions have a charge too large a charge and their RBE at the tumour is not optimal

1990: carbon ions are the ‘best’ compromise
Definition of RBE for a particular ‘end-point’

\[ RBE = \frac{D_{\text{x-ray}}}{D_{\text{particle}}} \]

- **RBE = 2**: Ion with no repair
- **RBE = 3**: Dose comparison for different types of radiation (ion vs. x-ray)
Light ions have a “qualitative” different effect

- **Photon**: RBE = 1
  - Mainly reparable SSB/DSB
  - “single/double strand breaks”

- **Carbon ion**: RBE = 3
  - 30-40 mm from the stopping point
  - Un-reparable multiple close-by double strand breaks (DSB) and clustered damages

Calculation of RBE needs physics + biology

GSI: LEM model
Effect of $\Delta E/\Delta x = \text{LET}$ on RBEs of many cells for many ‘end-points’

‘Radio Biological Effectiveness’

LET > 20 keV/µm = 200 MeV/cm = 40 eV/(2 nm)

Production of many unreparable localized double strand breaks and clustered damages
Yasuo Hirao

Hirohiko Tsujii
4000 pts 1994-2007

Pion therapy
Pion facilities

Los Alamos Meson Physics Facility (LAMPF) 209 pts 1974-1982

TRIUMPH at Vancouver 350 pts 1979-1994

PIOTRON at SIN (now PSI) 506 pts 1981-1993

TRIUMPH single pion channel

480 MeV protons

TRIUMPH single pion channel
"Orange Peel" spectrometer of the PIOTRON
60 SC coils and the support system of PIOTRON
Fig. 12 Scheme of the spot scan for irradiation of tumors with negative pions

For the irradiation of a tumor (T) which is larger than the small pion spot (Sp) and has an irregular shape, the patient (P) is embedded in solid material to obtain a cylindrical contour.
Conclusions on pion therapy

- 1000 patients treated at 3 facilities in 20 years
- The conformation to the tumour was not as expected
- The dose due to neutrons and low LET particles was not negligible
- The RBE was never larger than 1.5-2.0

- H. Blattmann (PSI) in 1993:
  “The initial hope to implement pions successfully in a hospital environment has definitely been given up”
In the years 1992-1994 the rate of progress changed rapidly:

1992 Loma Linda and Tsukuba complete the commissioning of their proton beams.

1993 The carbon ‘pilot project’ is launched by G. Kraft at GSI;

1993 MGH launches the tender for the first commercial proton facility;

1994 The last pion facility was stopped.

1994 The first patient is treated with a carbon beam at HIMAC;
First International Symposium on Hadrontherapy

Como, Italy
1993

All the actors presented their work and their ideas
## Ten years of tenders: from 1994 to 2004

<table>
<thead>
<tr>
<th>Year</th>
<th>Customer</th>
<th>Provider</th>
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<tbody>
<tr>
<td>1995</td>
<td>MGH, Boston MA, USA</td>
<td>IBA</td>
</tr>
<tr>
<td>1996</td>
<td>NCC, Kashiwa, Japan</td>
<td>SHI-IBA</td>
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<tr>
<td>1996-99</td>
<td>Tsukuba University</td>
<td>Hitachi</td>
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<td></td>
<td>Wakasa Wan Energy Research Center</td>
<td>Hitachi</td>
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<td></td>
<td>Shizuoka Prefecture</td>
<td>Mitsubishi</td>
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<tr>
<td>2001</td>
<td>PSI – Villigen, Switzerland</td>
<td>ACCEL</td>
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<tr>
<td></td>
<td>Wanjie Tumor Hospital – Zibo, China</td>
<td>IBA</td>
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<td>Chang An PMC – Beijing, China</td>
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<td>2002</td>
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<td>ACCEL</td>
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<td>Korean NCC - Seoul</td>
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<td></td>
<td>IUCF (MPRI), Bloomington IN, USA</td>
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<td>M.D. Anderson CC, Houston TX, USA</td>
<td>Hitachi</td>
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<tr>
<td>2004</td>
<td>University of Florida, Jacksonville FL, USA</td>
<td>IBA</td>
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Conventional radiotherapy
Orthovoltage (low energy) X-ray therapy began in January 1896. Many complications were seen because of the energy imparted to the skin.

Megavoltage (high-energy) radiation was added in the 50s. The high-energy X rays and Cobalt-60 gamma spared the skin.

**build-up**

6 MV photons are even better
1951 – first treatment at Victoria Hospital, London, Ontario

Cobalt-60 (1.2 MeV gammas)
has been produced for 50 years in CANDU reactors
by slow neutrons discovered by Fermi et al (1934)

Roy Errington
founder of MDS Nordion

Dr. Ivan Smith
After the World War II:
Old and new ‘cobalt bombs’

10 million patients treated with cobalt gamma rays
Important for developing countries
Electron linac

1939
Klystron invention

1947 - Stanford
The first linac for electrons
4.5 MeV and 3 GHz
In the world radiation oncologists use 10 000 electron linacs

40% of all the existing accelerators
Last 10 years: Intensity Modulated Radiation Therapy = IMRT...

... and now “Image Guided Radio Therapy” for organ motion

9 photon fields
Courtesy PSI

brain stem is the critical organ
The End