Cours/Lecture Series

1991 – 1992 ACADEMIC TRAINING PROGRAMME

SPEAKER : P. MANDRILLON / Laboratoire du Cyclotron, Nice, France
TITLE : High energy accelerators in medicine
TIME : 4 & 5 May from 11.00 to 12.00 hrs
PLACE : Auditorium

ABSTRACT

The treatment of tumours with charged particles, ranging from protons to ‘light ions’ (Carbon, Oxygen, Neon) has many advantages, but up to now has been little used because of the absence of facilities. After the successful pioneering work carried out with accelerators built for physics research, machines dedicated to this new radiotherapy are planned or already in construction. The rationale for this new radiotherapy, the high energy accelerators and the beam delivery systems are presented in these two lectures.
High energy accelerators in medicine

1. Historical background

2. Physical and biological rationale for heavy charged particles radiotherapy

3. Accelerators
   -α - the requirements
   β - Cyclotrons
     a ) neutrontherapy
     b ) protontherapy
     c ) light ion therapy
   γ - A linac for protontherapy
   δ - Synchrotrons
     a ) protontherapy
     b ) light ion therapy
   ε - Synchrotron versus cyclotron

4. Beam delivery systems

5. Gantries for heavy charged particles

6. Conclusions
   -α - some results of the EULIMA feasibility studies
   β - concluding remarks
   γ - references

P. Mandrillon
4/5 May 1992
Some basic books


2. The physics and radiobiology of fast neutron beams, D. Bewley
   1991, Medical science series

3. EULIMA Workshop on the potential value of light ion beam therapy
   Proceedings of the Workshop held in Nice in November 1988
   EUR-12165EN
   ==> available at the DG XII of the Commission of the European
   Communities, Brussels

4. Proceedings of the medical satellite meeting held during EPAC 90
   Nice, June 14-16, 1990, Editions Frontieres, Paris
historical background
A. Lacassagne

early history of radium therapy in the Institut de Radium de Paris

squamous carcinoma of cervix

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RADIOThéRapIE DES ÉPITHELIOMAS DU COL

**Tableau II**

<table>
<thead>
<tr>
<th>Nombre des années écoulées</th>
<th>Année 1919 (103 malades)</th>
<th>Année 1920 (85 malades)</th>
<th>Année 1921 (68 malades)</th>
<th>Année 1922 (95 malades)</th>
<th>Année 1923 (85 malades)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Guérisons</td>
<td>Morts par malade intermittent</td>
<td>Guérisons</td>
<td>Morts par malade intermittent</td>
<td>Guérisons</td>
</tr>
<tr>
<td>5 à 6</td>
<td>11</td>
<td>17</td>
<td>11</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>6 à 7</td>
<td>10</td>
<td>16</td>
<td>11</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>7 à 8</td>
<td>10</td>
<td>15</td>
<td>10</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>8 à 9</td>
<td>10</td>
<td>14</td>
<td>8</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>9 à 10</td>
<td>10</td>
<td>13</td>
<td>10</td>
<td>13</td>
<td>10</td>
</tr>
</tbody>
</table>

C) STATISTIQUE PAR STADE D'EXTENSION DES LÉSIONS, DES CAS TRAITÉS PAR RADIOTHÉRAPIE SEULE ÉTABLIE À LA FIN DE LA CINQUIÈME ANNÉE APRÈS LE TRAITEMENT. — Dans le tableau III se figurent que 350 malades, au lieu des 403 du tableau I. Les 53 malades diminués appartiennent à deux catégories :

a) 24 récidives postopératoires : 6 de la catégorie I (*) et 18 de la catégorie II (*). Ces malades se répartissent comme suit dans les cinq années envisagées : 8 en 1919, 7 en 1920, 1 en 1921, 4 en 1922, et 6 en 1923. Des 6 malades de la catégorie I, 3 ont été guéries; aucune des malades de la catégorie II n'a guéri.

b) 29 malades qui ont été traités par combinaison radium-chirurgicale. Elles se classent comme suit, au point de vue de leur répartition par années : 12 en 1919, 2 en 1920, 7 en 1921, 2 en 1922, et 6 en 1923. Au point de vue de leur répartition par stade d'extension des lésions et par résultat obtenu : 16 appartenaient au stade I (d'ont 7 ont guéri) ; 12 appartenaient au stade II (dont 4 ont guéri), une appartenait au stade IV.

Les 350 malades traités par radiothérapie seule, l'ont été en moyen des techniques suivantes : par curiéradiation intracavitária seule

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(*) Récidives localisées à la cicatrice.
(o) Récidives diffuses.
Some historical publications of Antoine Lacassagne between 1912 and 1931


Etudes histologiques et physiologiques des effets produits sur l'ovaire par les rayons X. Thèse Faculté de Médecine; Lyon. 26 Avril 1913.


Discussion à la Société de Chirurgie de Lyon sur "Quelques réserves sur le traitement du cancer par le Radium". Lyon Chirur., 1921, Mars, 18, p. 276.


In the USA, the story started in California in Berkeley.

On the picture, many famous accelerator physicists and physicians... in the yoke of the 60" cyclotron.

Some historical publications of the Berkeley group between 1934 and 1940

Lawrence, E.O.

Chievitz, O. and Hevesy, G.

Lawrence, J.H. and Lawrence, E.O.

Lawrence, J.H. and Tennant, R.

Hertz, S., Roberts, A. and Evans, R.D.

Lawrence, J.H.

Stone, R.S., Lawrence, J.H. and Aebersold, P.C.
The pioneering work with charged particles

1946. R. Wilson "Radiological use of fast protons"
Radiology 47, 487 (1946)
⇒ 1st characterization of beams of protons predicting
that they should be useful: little scattering and
definite range in which the dose increases with depth.

1952. C. Tobias, H. Anger and J. Lawrence
"Radiobiological use of high energy deuterons and"
American Journal of Roentgenology 64 : 1 (1952)
⇒ Experimental confirmation of Wilson views.
The authors used the 190 NeV d from the 184° Sc.

1956. C. Tobias, J. Roberts and J. Lawrence
"Irradiation hypophysectomy and related studies
using 340 NeV p and 190 NeV d" Proceedings
of the Int. Conf on Peaceful uses of Atomic Energy
held in Geneva in the United Nations.
⇒ 1st therapeutic use of ion beams where the
authors tried to destroy the endocrine function
of the pituitary in patients with metastatic
carcinoma of the breast.
II

The physical and biological rationale
Visual Representation of Effects of Various Beams

A comparison of the effects of three types of therapy beams in the treatment of a tumor approximately 10 cm from the surface of the body. Some characteristics:

The $^{60}$Co gamma beam is most effective (100%) just beneath the surface of the skin; usually most damage will occur here, not at the site of the tumor, where the dose is significantly smaller. Radiation damage may also occur beyond the tumor, since the gamma rays cannot be "stopped" at the tumor. The beam is also spread laterally beyond the aperture through which it is delivered. Hypoxic tumor tissues are much more resistant to gamma rays than oxygenated tissues.

The proton beam is more effective than the gamma beam at the site of the tumor and does not extend beyond the tumor site into normal tissues. However, its maximum effect (100%) covers a smaller portion of the tumor than the carbon beam. While the spread of the beam beyond the aperture is significantly less than for the gamma beam, there is still some spreading of the beam into tissue surrounding the tumor; this is greater than with the carbon beam. Like gamma rays, protons are not effective in dealing with hypoxic tumors.

The carbon beam is precisely delivered to the site of the tumor. Its maximum effect (100%) virtually covers the tumor area and nearby normal tissues receive minimal radiation. There is little spreading of the beam beyond the diameter of the aperture, but the dose immediately beyond the tumor is greater than in the case of protons. Heavier ions (e.g., neon, silicon) are effective in decreasing the difference of sensitivity between oxygenated and hypoxic tumor cells.
Cross section of a man with a prostate tumour (centre, ringed in green): X-rays leave most energy in the hips, protons are on target.
About the Bragg peak

As an ion of charge \( Z \) velocity \( v \) passes a quasi-stationary electron in the medium, the momentum transferred (foremost) is proportional to \( Z \times \frac{1}{v} \). Therefore, the energy transfer is proportional to \( Z^2 \times \frac{1}{v^2} \).

Hence, the ionization density (i.e., LET, linear energy transfer) rises as the track slows down, until at the very end of the range, the ionic charge is reduced by \( e^- \) pick-up and the ionization falls rapidly to 0.

\[ \Rightarrow \] This gives rise to the Bragg peak: the maximum dose is delivered in a narrow peak at the end of the range.

The \( Z^2 \) dependence means that for equal velocities, the ionization density for O ions \((Z=8, A=16)\) is 64 times greater than for protons. But it only has 16 times the kinetic energy so the range will be 4 times less!

\[ \Rightarrow \] Much higher energies are needed to achieve the same required to reach deep-seated tumors.
Fig. 7. Energy-range curves showing the depth to which various ions will penetrate in tissue.
Depth dose curve in I.E. plastic for oxygen ions of 408 MeV/nucleon

See recommended TIS-RP/TH 30.9

Measured at LEAR on 16/14/89 by C. Kessler, A. Sullivan, and G. Tuttle
The ionisation increases as the particles slows down giving a greater dose at depth than on the surface (top figure). In practice, the Bragg peak should be spread out to fit the tumour volume (bottom figure).
Nuclear fragmentation of a 400 MeV/n $^{20}$Ne beam

Measured at GSI by I. Schull, D. Scharf and G. Kraft

Fig. 2. Top: Bragg curve obtained from detector D3 which gave best performance among the stack detectors. A water-equivalent of 2.8 mm for the three silicon detectors is included in the water depth. The $^{20}$Ne beam energy at the entrance of the water phantom was 396 MeV/u.

Bottom: Attenuation of primary neon particles as a function of depth in water.

Approximately 40% of the primary neon particles survive the complete stopping process and reach the Bragg maximum!
Fig. 3. Counting rate vs. energy loss signals in detectors D1 and D3 registered at a depth of 23 mm water. The main peak at about 30 MeV is caused by the primary $^{20}$Ne particles. Projectile fragments which are produced in the water target move at about the same mean velocity as the primary beam particles. According to their lower charge number $Z$, they are observed at smaller energy loss values which scale approximately with $Z^2$.

Fig. 4. Two-dimensional plot of coincident energy loss signals in detectors D1 and D3 registered at a depth of 23 mm water. The main peak at about 30 MeV is caused by the primary $^{20}$Ne particles. Projectile fragments which are produced in the water target move at about the same mean velocity as the primary beam particles. According to their lower charge number $Z$, they are observed at smaller energy loss values which scale approximately with $Z^2$. Beyond the Bragg maximum only secondaries are observed which have larger range values according to their lower atomic numbers.
Most biological effects of radiation can be interpreted in terms of the effects on individual cells. Cellular survival curves are therefore basic to an understanding of radiobiology. Figure 7.1 is an example and shows the survival of cells of human malignant origin to neutrons and x-rays, exposed under aerobic and hypoxic conditions (from Nias et al 1967). Three differences between the effects of neutrons and x-rays are immediately evident.

1. Neutrons have an RBE greater than one relative to x-rays.
2. The survival curves are more nearly exponential.
3. The modifying effect of hypoxia is smaller, i.e., the oxygen enhancement ratio (OER) for neutrons is smaller than for photons.

Fast neutrons are classified as high LET particles because of the high ionisation density of the recoil particles (p, d...).
Oxygen Enhancement Ratio and Relative Biological Efficiency versus Linear Energy Transfer. The range of LET available with H, C, and Ne is indicated.

- High LET radiations exhibit differences in their biological effects to low LET.

1. Reduction in the differences in radio-sensitivity for different types of cell.

2. Less repair phenomena and, as a consequence, less difference between the responses of the cell populations to fractionated irradiation.

3. All cell populations, in all conditions, tend to respond more similarly to high LET radiation than to low LET.

Important consequences for hypoxic cells which are less sensitive to radiation and therefore at the center of larger poorly vascularized tissues. The oxygen effect is less important for high LET particles.
Extended Bragg peak for various ions. Solid line: physical dose; dotted line: biologically effective dose allowing for increased RBE. Peaks are shown extended to 4cm (left) and 12cm (right).

III

Accelerators
The choice of the accelerator for heavy charged particle radiotherapy is strongly dependent on the medical requirements, the costs i.e. the so called socio-economical aspects, and technological choices for a hospital-based facility. The main requirements could be summarised as follows:

1 - Installed in a large hospital in order to get an adequate supply of medical and scientific staff for developing high technical level diagnosis and treatment systems.

2 - Accelerator highly reliable, easy to operate and short repair time.

3 - Beam delivery system permitting to scan the beam over the tumour volume.

4 - Avoiding to move the patient, i.e. possibility to use different directions of the beam: horizontal and vertical beams, either above or below the couch. A variable incidence beam (the so called rotating gantry by the physicians) is suitable if the maximum beam rigidity makes this requirement realistic.

5 - Range in tissues: minimum 3 cm, typical 20 cm, maximum 25 cm. This specification fixes the energy range.

6 - Maximum dose rate at the tumour: 5 Gray/minute in a 2 liter volume. This fixes the maximum intensity (cf. Table 1 below).

7 - Maximum irradiated field: 30 x 30 cm².

8 - For a light ion therapy facility, possibility to check the treatment plans by Positron Emission Tomography (PET) of the irradiated volume. This is easy with radioactive beams such as C¹¹, N¹³, O¹⁵ produced by fragmentation of light ions. In a later phase, use of these beams for treatment could be considered.

The energies and magnetic rigidity for 20 cm range are given in Table 1. The magnetic rigidity fixes the bending radius of the particles, and therefore determines the size of the accelerator and the beam delivery system. The number of particles per second (pps) required to deliver a dose of 5 Gray over a volume of two litres in one minute is given in the final column.

<table>
<thead>
<tr>
<th></th>
<th>Energy MeV/n</th>
<th>Magnetic rigidity Tm</th>
<th>Intensity required pps</th>
</tr>
</thead>
<tbody>
<tr>
<td>p</td>
<td>175</td>
<td>2.00</td>
<td>2.10¹⁰</td>
</tr>
<tr>
<td>He</td>
<td>175</td>
<td>4.00</td>
<td>5.10⁹</td>
</tr>
<tr>
<td>C</td>
<td>330</td>
<td>5.67</td>
<td>10.⁹</td>
</tr>
<tr>
<td>O</td>
<td>380</td>
<td>6.36</td>
<td>2.10⁹</td>
</tr>
<tr>
<td>P²⁺</td>
<td>470</td>
<td>6.96</td>
<td>5.10⁵</td>
</tr>
</tbody>
</table>
Positron emitting isotopes (\(^{15}\text{O}, \^{10}\text{C}, \^{11}\text{C}, \^{13}\text{N}, \^{19}\text{Ne}\)) can be produced by the spallation of accelerated nuclei in tissues or by actually accelerating beams of the short half-life positron emitters to specific energies. These beams will stop in a small volume of tissue at a depth which depends on the energy. Photons are released when the positron encounters an electron which is usually at the Bragg peak position. These annihilation photons are used to spatially locate the position of the beam using positron tomography.

![Image of the treatment plan for neon where the stopping beam is adjusted in range to avoid the spinal cord.](image)

*Courtesy of LBL to illustrate point 8 of the medical requirements!*
Table 2: Protontherapy facilities in 1992

<table>
<thead>
<tr>
<th>Institution, Place</th>
<th>First treatment</th>
<th>Last treatment</th>
<th>Treated patients (date of total)</th>
<th>Accelerator type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berkeley-184, California (USA)</td>
<td>1955</td>
<td>1957</td>
<td>30</td>
<td>synchrocyclotron</td>
</tr>
<tr>
<td>Uppsala (Sweden) (1)</td>
<td>1957</td>
<td></td>
<td>96</td>
<td>synchrocyclotron</td>
</tr>
<tr>
<td>Harvard, Mass. (USA)</td>
<td>1961</td>
<td></td>
<td>5419</td>
<td>synchrocyclotron</td>
</tr>
<tr>
<td>Leningrad (USSR) (1)</td>
<td>1964</td>
<td>1974</td>
<td>97</td>
<td>synchrocyclotron</td>
</tr>
<tr>
<td>Moscow (USSR)</td>
<td>1969</td>
<td></td>
<td>2200</td>
<td>synchrocyclotron</td>
</tr>
<tr>
<td>Chiba (Japan)</td>
<td>1975</td>
<td></td>
<td>719</td>
<td>synchrocyclotron</td>
</tr>
<tr>
<td>Tsukuba (Japan)</td>
<td>1979</td>
<td></td>
<td>74</td>
<td>synchrocyclotron</td>
</tr>
<tr>
<td>PSI (Switzerland)</td>
<td>1983</td>
<td></td>
<td>242</td>
<td>synchrocyclotron</td>
</tr>
<tr>
<td>Clatterbridge (UK)</td>
<td>1984</td>
<td></td>
<td>1150</td>
<td>isochronous cyclotron</td>
</tr>
<tr>
<td>Loma Linda, California (USA)</td>
<td>1989</td>
<td></td>
<td>189</td>
<td>isochronous cyclotron</td>
</tr>
<tr>
<td>Louvain-La-Neuve (Belgium)</td>
<td>1990</td>
<td></td>
<td>76</td>
<td>isochronous cyclotron</td>
</tr>
<tr>
<td>Nice (France)</td>
<td>1991</td>
<td></td>
<td>9</td>
<td>isochronous cyclotron</td>
</tr>
<tr>
<td>Orsay (France)</td>
<td>1991</td>
<td></td>
<td>47</td>
<td>isochronous cyclotron</td>
</tr>
</tbody>
</table>

(1) These synchrotrons were stopped for improvements during several years.

T3/CERN - intro lead. 2
Neutrontherapy

The early work was carried out by Stone, Lawrence and Larkin between 1938 and 1942 in Berkeley, but there was no basic biological information available at that time to provide a rationale for the use of neutrons in preference to X-rays. Further the energy was too small in order to get a good dose distribution. Although a few advanced tumours were cured, there was an unexpectedly high incidence of late radiation morbidity which led to the abandonment of neutrontherapy.

A renewed interest occurred in the late 50ties following a great deal of radiological work which had demonstrated possible explanations for the radioresistance of tumours (OER). Fast neutrons are classified as high LET particles because of the recoil particles (protons, alpha).

Following the work carried out during many years in the Hammersmith hospital in London (Mary Catteral, David Bewley) the requested performances of the cyclotrons are now well known:

- Average energy of the neutron spectrum about 20 Mev which means energy of the primary (proton or deuteron) beam up to 50-60 Mev

- Average intensity requested to provide the flux is dependant on the distance between the target (thick Beryllium) and the patient: for 1.50 meter (necessary for the collimator) 15 microamps are necessary.
Fig. 7: Median plane view of the K 100 MSU

\[ K = \frac{e^2 c^2}{2 M u c} (Bp)^2 = 48.24 (Bp)^2 \]

- Neglecting relativistic terms: \( \frac{T}{A} = K (Z/A)^2 \)
- General: \( \frac{T}{A} = M u c \left\{ \sqrt{1 + \frac{2 K}{M u c (A^2)} Z^2} - 1 \right\} \)
  
  ex: \( K(\text{CERN}) \approx 800 \text{MeV} \) (but not NeV for protons)
K100 SUPERCOND. CYCLOTRON

Designed by H. Blosser, from NSCL of MSU for the radiation oncology center of Harper Hospital/Detroit

<table>
<thead>
<tr>
<th>Accelerated particle</th>
<th>deuterons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max. energy</td>
<td>40 Mev</td>
</tr>
<tr>
<td>Central field</td>
<td>4.6 Tesla</td>
</tr>
<tr>
<td>Frequency</td>
<td>105 Mhz</td>
</tr>
<tr>
<td>Acceleration</td>
<td>3rd harmonic</td>
</tr>
<tr>
<td>Max orbit radius</td>
<td>30 cm</td>
</tr>
<tr>
<td>Internal central source</td>
<td></td>
</tr>
<tr>
<td>Internal neutron production target</td>
<td></td>
</tr>
</tbody>
</table>

Special features

Rotating cyclotron which involves a pair of 4.2 m diameter rings mounted on rollers, with a counterweight opposite the cyclotron to balance the system and a patient table cantilevered onto the axis of the ring system from the adjacent fixed floor.

With this structure the cyclotron can rotate through a full 360 deg. relative to the patient, hence avoiding a rotating gantry.

advantage: no heavy collimator
no gantry

disadvantage: large cyclotron room!!
MEDICYC: 65 MeV H- cyclotron
Some parameters of MEDICYC

- Accelerated particles: $^1$H$^-$ / cesp source
- Maximum energy: 65 keV
- Extracted current:
  - proton therapy: $\sim 100\mu A$
  - neutron therapy: $\sim 20\mu A$
  - $^{18}F$ production: $\sim 5/10\mu A$
- Room temperature magnet
  - pole diameter: 1.6 m
  - 4 sectors
  - weight: 130 tons
- 2 accelerating cavities
  - RF freq: 25 MHz
  - Peak voltage: 55 kV
- Extraction
  - 2 strippers for simultaneous extraction for diagnostic line and radiotherapy line
The "CYCLONE 230"
proposed by IBA