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pt. 1

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

Acad. Train.
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pt. 1

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.

24/2613

Div. DG/PU
Distr. int. & ext.

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

- 1. Heavy particle radiotherapy, M.R. Raju, 1980, London Academic**
- 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**

I

historical background

A. Lacassagne
early history of radiotherapy
in the Institut de radium à Paris
squamous carcinoma of cervix

RADIOTHÉRAPIE DES ÉPITHÉLIOMAS DU COL

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TABLEAU II

Nombre des années écoulées	ANNÉE 1919 (103 MALADES)			ANNÉE 1920 (98 MALADES)			ANNÉE 1921 (48 MALADES)			ANNÉE 1922 (69 MALADES)			ANNÉE 1923 (85 MALADES)		
	Guérison	Récidive	Mort par maladie intercurrente	Guérison	Récidive	Mort par maladie intercurrente	Guérison	Récidive	Mort par maladie intercurrente	Guérison	Récidive	Mort par maladie intercurrente	Guérison	Récidive	Mort par maladie intercurrente
5 à 6	II			17			II		I	17			26		
6 à 7	10		I	16		I	II			17					
7 à 8	10			15		I	10		I						
8 à 9	10			14		I									
9 à 10	10														

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 ne figurent que 350 malades, au lieu des 403 du tableau I. Les 53 malades éliminées appartiennent à deux catégories :

a) 24 récidives postopératoires : 6 de la catégorie I ⁽¹⁾ et 18 de la catégorie II ⁽²⁾. Ces malades se répartissent comme suit dans les cinq années envisagées : 8 en 1919, 7 en 1920, 1 en 1921, 4 en 1922, et 4 en 1923. Des 6 malades de la catégorie I, 3 ont été guéris; aucune des malades de la catégorie II n'a guéri.

b) 29 malades qui ont été traitées 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 (dont 7 ont guéri) ; 12 appartenaient au stade II (dont 4 ont guéri), une appartenait au stade IV.

Les 350 malades traitées par radiothérapie seule, l'ont été au moyen des techniques suivantes : par curiethérapie intracavitaire seule

(1) Récidives localisées à la cicatrice.
(2) Récidives diffuses.

Some historical publications of Antoine Lacassagne
between 1912 and 1931

Action nocive des rayons X sur le tube digestif. (En collaboration avec Cl. REGAUD et Th. NOGIER). Paris Médical. 19 Octobre 1912, T. 8, p. 489-491.

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

Actions des rayons du radium sur les muqueuses de l'oesophage et de la trachée chez le lapin. C.R. Soc. Biol. 8 Janvier 1921, 84, p. 26.

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.

Immuabilité de la structure dans les récidives locales successives des cancers traités par les radiations. C.R. Soc. Biol. 10 Mars 1923, T. 88, p. 599.

De la résistance des leucocytes du sang vis à vis des rayons X. (en collaboration avec J. JOLLY). C. R. Soc. Biol. 7 Juillet 1923, T. 89, p. 379.

- Méthode auto-historadiographique pour la détection dans les organes du pollonium injecté (en coll. avec J. LATTES). C. R. Acad. Sc. 28 Janvier 1924, T. 178, p. 488.

Action directe et indirecte des radiations sur les tissus cancéreux. Radiophysiologie et Radiothérapie, 1928, T. 1 p. 401.

- La radiothérapie des épithéliomas du col utérin à l'Institut du Radium de Paris. Radiophysiologie et Radiothérapie. 1929, T. 2, p. 95-131.

Quelques cas de sarcomes de l'utérus traités par les méthodes radiothérapiques (en coll. avec Cl. REGAUD). Radiophysiologie et radiothérapie. 1930. T. 2, p. 247-271.

Action des rayons alpha sur Polytoma-Uvella. Détermination des "cibles" correspondantes aux principales lésions observées. (en coll. avec F. Holweck). C.R. Soc. Biol. 20 Juin 1931, T. 107, p. 812.

Essai d'interprétation quantique des diverses lésions produites dans les cellules par les radiations. (En coll. avec F. Holweck). C.R. Soc. Biol. 20 Juin 1931, T. 107, p. 814.

- Résultats obtenus à l'Institut du Radium de Paris en radiothérapie des cancers du rectum. Radiophysiologie et Radiothérapie. 1931, T. 2, p. 577-585.

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.

(Left to right and top to bottom): A.S. Langsdorf, S.J. Simmons, J.G. Hamilton, D.H. Sloan, J.R. Oppenheimer, W.M. Brobeck, R. Cornog, R.R. Wilson, E. Viez, J.J. Livingood, J. Backus, W.B. Mann, P.C. Aebersold, E.M. McMillan, E.M. Lyman, M.D. Kamen, D.C. Kalbfell, W.W. Salisbury, J.H. Lawrence, R. Serber, F.N.D. Kurie, R.T. Birge, E.O. Lawrence, D. Cooksey, A.H. Snell, L.W. Alvarez, P.H. Abelson.

Some historical publications of the Berkeley group
between 1934 and 1940

Lawrence, E.O.

Radioactive Sodium Produced by Deuteron Bombardment. Phys. Rev. 46: 746-747 (1934).

Chievitz, O. and Hevesy, G.

Radioactive Indicators in the Study of Phosphorus Metabolism in Rats. Nature 136: 754-755 (1935).

• Lawrence, J.H. and Lawrence, E.O.

The Biological Action of Neutron Rays. Proc. Natl. Acad. Sci. 22: 124-133 (1936).

Lawrence, J.H. and Tennant, R.

Comparative Effects of Neutrons and X-rays on Whole Body. J. Exper. Med. 66: 667-688 (1937).

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

Radioiodine as Indicator in Study of Thyroid Physiology. Proc. Soc. Exper. Biol. and Med. 38: 510 (1938).

Lawrence, J.H.

Nuclear Physics and Therapy: Preliminary Report on a New Method for the Treatment of Leukemia and Polycythemia. Radiology 35: 51-59 (1940).

• Stone, R.S., Lawrence, J.H. and Aebersold, P.C.

Preliminary Report on Use of Fast Neutrons in Treatment of Malignant Disease. Radiology 35: 322-327 (1940).

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 KeV d from the 184th SC.

- 1956 C. Tobias, J. Roberts and J. Lawrence
"Irradiation hypophysectomy and related studies using 340 KeV p and 190 KeV 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.

X-RAY BEAM

PROTON BEAM

Loma Linda

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 (for ext time) is proportional to $Z \times \frac{1}{v}$. Therefore the energy transf. is proportional to Z^2/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 ionisation falls rapidly to 0.

⇒ 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 ionisation 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!

⇒ much higher energies are needed to achieve the same dose required to reach deep-seated tumours!

Range-Energy Curves

Fig. 7. Energy-range curves showing the depth to which various ions will penetrate in tissue.

Measured at LEAR on 16/11/89 by E. Raffinse, A. Sullivan and J. Tugby
see memorandum T15-RP/TH 90-01

DEPTH DOSE CURVE IN T.E. PLASTIC FOR OXYGEN IONS OF 408 MeV/NUCLEON
(10^5 IONS/sec)

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/u ^{20}Ne beam

Measured at GSI by I. Schall, D. Schardt 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!

Fragments spectra

Fig.3. Energy loss spectra measured with the ΔE_1 detector set up in water. The values of ΔE_1 are in MeV. The spectra show the effect of increasing depth on the energy loss spectra. The spectra show that as the depth increases, the energy loss spectra shift to higher values and the number of lighter secondary particles increases. Beyond the Bragg maximum only secondaries are observed which have larger range values according to their lower atomic numbers.

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 .

(*) MULTIPLE RUTHERFORD COLLISIONS OF PARTICLES ON TARGET NUCLEI

$$\sigma_x, \sigma_y \propto \frac{1}{\sqrt{M_{\text{particle}}}}$$

XBL811-3516

FIG. 2

Figure 7.1. Survival curves of HeLa cells to x-rays and 14 MeV neutrons in air and nitrogen. From Nias *et al* (1967), reproduced by permission of the authors and of Taylor and Francis Ltd.

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, α ...)

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).
 (from Hall: *Br.J.Radiol.*, 54,773, 1981)

Accelerators

3. 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 : $30 \times 30 \text{ cm}^2$.

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 C^{11} , N^{13} , O^{15} 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 1

	Energy	Magnetic rigidity	Intensity required
	MeV/n	Tm	pps
P	175	2.00	2.10^{10}
He	175	4.00	5.10^9
C	330	5.67	10^9
O	390	6.84	7.10^8
Ne	470	6.98	5.10^8

Positron emitting isotopes (^{15}O , ^{10}C , ^{11}C , ^{13}N , ^{19}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.

Courtesy of LBL

to illustrate point 8 of the medical requirements!

Table 2 : Protontherapy facilities in 1992

Institution, Place	First treatment	Last treatment	Treated patients (date of total)		Accelerator type
Berkeley-184, California (USA)	1955	1957	30		synchrocyclotron
* Uppsala (Sweden) (1)	1957		96	Nov. 1991	synchrocyclotron
Harvard, Mass. (USA)	1961		5 419	Dec 1991	synchrocyclotron
* Dubna (USSR) (1)	1964	1974	97	May 1991	synchrocyclotron
Moscow (USSR)	1969		2 200	Dec 1991	synchrotron
Leningrad (USSR)	1975		719	Jun 1991	synchrocyclotron
Chiba (Japan)	1979		74	May 1991	isochronous cyclotron
Tsukuba (Japan)	1983		242	Aug. 1991	synchrotron
PSI (Switzerland)	1984		1 150	Nov. 1991	isochronous cyclotron
Clatterbridge (UK)	1989		189	Dec. 1991	isochronous cyclotron
Loma Linda, California (USA)	1990		76	Dec. 1991	synchrotron
Louvain-La-Neuve (Belgium)	1991		9	Dec. 1991	isochronous cyclotron
Nice (France)	1991		47	Dec. 1991	isochronous cyclotron
Orsay (France)	1991		13	Dec. 1991	synchrocyclotron

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

①

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 Catterall, 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 = electron energy parameter expressed in MeV

$$K = \frac{e^2 c^2}{2 m_{uc}^2} (B\rho)^2 = 48.24 (B\rho)^2$$

• Neglecting relativistic terms : $T/A = K (Z/A)^2$

• General : $T/A = m_{uc}^2 \left\{ \sqrt{1 + \frac{2K}{m_{uc}^2} \left(\frac{Z}{A} \right)^2} - 1 \right\}$

ex : $K(\text{CERN SE}) \approx 800 \text{ MeV}$ (but 600 MeV protons!)

K100 SUPERCOND. CYCLOTRON

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

Accelerated particle	deuterons
Max. energy	40 Mev
Central field	4.6 Tesla
Frequency	105 Mhz
Acceleration	3 rd harmonic
Max orbit radius	30 cm
Internal central source	
Internal neutron production target	

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: 1 cyclotron / room!!

MEDICYC, Nice, 65 MeV H^- cyclotron
 for neutrino therapy, $\bar{\nu}_e$ energy production, μ and F^{18} production

MEDICYC : 65 Mev H^- cyclotron

Some parameters of MEDICYC

- Accelerated particles = H^+ / cusp source
axial injection
- Maximum energy : 65 MeV
- Extracted current : proton therapy $\sim 100 \mu A$
neutron therapy $\sim 20 \mu A$
 F^{18} production $\sim 5/10 \mu A$
- Room temperature magnet
 - pole diameter 1.60 m
 - 4 sectors
 - weight 130 tons
- 2 accelerating cavities
 - RF freq 25 MHz
 - Peak voltage 55 Kvolts
- Extraction
 - 2 strippers for simultaneous extraction
for diagnostic line and radiotherapy line

② Cyclotrons for heavy charged particle

The "CYCLONE 230"
proposed by IBA