Title
UNCONVENTIONAL RADIATIONS IN RADIOTHERAPY

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UNCONVENTIONAL RADIATIONS IN RADIOTHERAPY

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I will make a brief presentation of physical and radiobiological aspects of unconventional radiations. [Neutrons: thermal and fast heavy charged particles; protons: helium ions and π^- mesons (see Fowler 1964)]. Dr. Max Boone will be talking on fast neutrons and Dr. Hutson on π^- beams in radiotherapy later in this symposium.

I see you have a problem to have a talk on unconventional radiations with unconventional pronunciation. So please bear with me.

Localization of dose in the region of interest and minimization of the unavoidable dose to the surrounding normal tissues is one of the essential requirements in radiotherapy. The dose that can be delivered to the tumor is in general limited by the normal-tissue injury. Normal-tissue injury depends on the volume irradiated: the smaller the volume, the greater the dose the normal tissue can likely withstand. Any radiation that improves dose-localization characteristics is of potential interest in radiotherapy. Significant progress has been madein cure rates with the advent of megavoltage sources of radiation (Kaplan 1969). In spite of these developments failure to cure is still common. The failure to cure is generally due to the inability to give tumoricidal doses without undue reactions to normal tissue, and this could be partly due to the presence of hypoxic cells in the tumor. Gray (1961) postulated that hypoxic cells may be an important cause

of failure to cure by conventional radiotherapy. It is now known, however, that in certain types of animal tumors and therefore probably in human tumors as well, an increasing proportion of hypoxic cells of the tumor become oxygenated during fractionated radiotherapy (Van Putten and Kallman 1968, Thomlinson 1966). It may therefore be possible to overcome the oxygen effect by fractionation with conventional radiation alone for some less advanced stages of cancer, but there is little evidence for oxygenation in advanced cancer (see Van Den Brenk 1969).

When cells are exposed to highly ionizing radiations, such as neutrons and low-energy heavy charged particles, the presence or absence of oxygen in the cells does not make as much difference in their radiation sensitivity as in the case with conventional radiation. Now let us look into different radiations with regard to their dose-localization characteristics and to dealing with the hypoxic cell problem.

Fast neutrons were first tried in radiotherapy in the year 1938, 6 years after the discovery of neutrons. It was not known at that time that fast neutrons are effective in significantly overcoming the oxygen effect, and very little was known about the biological effects of fast neutrons. The early trials were not successful.

However, with the current understanding of radiobiology of fast neutrons, there is hope that fast neutrons may be of value in cases in which hypoxic cells are a limiting factor when conventional radiation is used. Fast neutron therapy is being reevaluated at Hammersmith Hospital, London (see Bewley 1970), and a few centers in this country are also planning similar work.

Neutron-capture therapy was tried at Brookhaven National Laboratory and at the MIT reactor for the treatment of brain tumors (see Brownell et al. 1967) This form of therapy takes advantage of a physical and biochemical phenomenon. Thermal neutrons have a very high probability for reaction with a nonradioactive isotope of boron, ^{10}B, which after capturing a thermal neutron breaks into a lithium ion and an α particle. The lithium ion and an α particle between them share an energy of 2.8 MeV, and they are highly ionizing; the oxygen-enhancement ratio for these products is nearly unity. Due to the breakdown of blood brain barrier, tumor tissue loses the selective capacity of taking chemicals from the blood stream. Hence, when a compound incorporated with ^{10}B is injected into the blood stream, it is taken up by the tumor tissue but not by normal tissue. Thus, when a patient injected with a compound containing ^{10}B is exposed to a thermal neutron beam from a reactor, it is possible in principle to cause selective damage to the tumor tissue in the brain. The unique feature of this technique is that destruction of cancer occurs from within the cancer cells, because the boron compound localizes in the cancer cells only. Furthermore, it is not necessary to know the precise location of the cancer cells; the boron gets into the cancer cells. Although the principle was exciting, it did not give successful results, partly because the boron compound was found to concentrate in the blood also, thereby causing radiation damage to the blood capillaries in the brain. The future for this therapy awaits in getting a boron compound that leaves the blood and concentrates mainly in the cancer cells.

Charged particles that are many times as heavy as electrons are called heavy charged particles. They have the property of delivering more dose at depth than at the surface, and practically zero dose a short distance beyond the range. This is because when a heavy-charged-particle beam passes through a medium, most of the

particles remain in the beam. They lose energy mainly through Coulomb interactions with electrons in the medium without being lost from the beam in such interactions. The particles in the beam slow down as they pass through the medium. The rate of energy loss of the charged particle is proportional to the square of its charge and approximately inversely proportional to the square of its velocity. Thus, the dose delivered by a heavy charged particle beam increases with depth, giving rise to a sharp maximum known as the Bragg peak near the end of the range. Electron beams have no Bragg peak because the statistical distribution of electron stopping points is quite broad. In addition the lack of Bragg-peak effect for electrons is the velocity of electrons remains nearly relativistic (hence the energy loss remains very nearly the same) during most of the path.

High-energy x rays have better skin-sparing effects and depth-dose distribution than low-energy x rays. As x rays pass through medium they interact with electrons in the medium, are exponentially attenuated rapidly, and are lost from the beam. Fast neutrons, in their interaction with medium, release heavy particles (protons, deuterons, α particles, or recoiling nuclei), whereas x rays release electrons. The neutrons also are rapidly attenuated exponentially when they travel through medium, as are x rays, but unlike heavy charged particles. Thus the dose deposited by x rays and neutrons, except for initial buildup, decreases with depth. From physical considerations, heavy charged particles surpass conventional radiations and fast neutrons in delivering tumoricidal doses to deep-seated tumors with minimum dose to the surrounding tissue.

Heavy charged particles such as protons and helium ions are accelerated synchrocyclotrons, which produce monoenergetic beams.

These beams produce sharp Bragg peaks of insufficient width for most radiotherapeutic applications. However, the dose at the peak can be made uniform over a broad range by overlapping a series of Bragg peaks, with progressively smaller intensities and shorter ranges, by using a composite absorber called a ridge filter (Larsson 1961; Karlsson 1964). Such a modified depth-dose distribution of monoenergetic heavy charged particles is useful for uniform irradiation of a large volume. With this modification, the ratio of the dose at the peak to the dose at the entrance is reduced with increasing thickness of the treatment volume.

Negative π^- mesons are also heavy charged particles, and they have approximately 15% of the mass of a proton. Thus they share the properties of heavy charged particles mentioned before. In addition, they have the unique property of being captured by a nucleus of the medium when they come to rest. The captured nucleus breaks apart into highly ionizing fragments, some of which have ranges less than 1 mm. Thus these fragments enhance the dose at the Bragg peak; in addition they are expected to overcome the oxygen effect considerably.

The calculated depth-dose distribution of different radiations normalized to a uniform dose over 5 cm at a mean depth of 10 cm is shown in Fig. 1. Depending on the energy of neutrons, their depth-dose distribution in between those of 250-kV x rays and of ^{60}Co γ rays.

It can be seen that π^- mesons have the most favorable depth-dose distribution. However, the sharpness of dose cutoff beyond the peak is not so good as for protons and helium ions. Contamination in the pion beam and neutrons from stars further reduce the sharpness. The entrance dose required for a given dose at the peak is somewhat higher for helium ions than for protons, and for ions heavier than

helium it is higher yet. It must be noted that the dose at the entrance for a given dose at the peak increases with increasing thickness of the treatment area. However, the dose at the peak for the treatment area of any thickness at any desired depth is never lower than at the entrance.

Significant improvements in cure rates and in reducing complications have resulted from the advent of high-energy x rays and electrons. On this basis we can expect further improvements with heavy charged particles because of their superior depth-dose distribution. Therapeutic use of protons in this country has been mainly at the Harvard University cyclotron, and of helium ions at the 184-inch synchrocyclotron at Berkeley. Therapeutic use of these two facilities has been mainly for pituitary irradiation of patients with acromegaly, diabetic retinopathy, and Cushing's disease (Lawrence and Tobias 1965). These facilities, however, are not extensively used for radiotherapy. The cyclotron at Uppsala is being used to a limited extent for radiotherapy. More and more cyclotron centers, both in this country and in the Soviet Union, are currently planning to have biomedical facilities for therapy at their cyclotrons.

The biological effects of protons at different depths of penetration, such as shown in the figure, are not significantly different from conventional radiation (see Larsson et al. 1960), hence clinical experience gained with conventional radiation can be applied to proton radiotherapy. For helium-ion beam the relative biological effectiveness as measured with cells in culture at the peak region (Fig. 1) is about 30% greater than at entrance, and the oxygen-enhancement ratio is about 2 (Raju et al. 1971). The biological effects before the peak region are not significantly different from conventional radiation.

Hence the helium-ion beam offers the dose-localization characteristics of protons, and in addition the hypoxic cell problem may also be partly overcome. Ions heavier than helium are expected to overcome the hypoxic-cell problem even better (Tobias et al. 1971).

The biological effects of π^- mesons for a beam of depth-dose distribution such as shown in Fig. 1 are not yet measured, because of the limitation of intensities now available. However, the biological effects of π^- mesons were measured in various biological systems at the narrow peak ($\approx$ 2 cm) of depth-dose distribution (Raju and Richman 1970). From these results, one can expect higher RBE and lower OER at a broad peak such as shown in the figure than for helium ions.

In summary, one can expect significant improvements in the results of radiotherapy if heavy charged particles are used. The clinical experience gained with protons and helium ions is very helpful for eventual use of π^- mesons in radiotherapy.

REFERENCES

D. K. Bewley, Fast Neutron Beams for Therapy, in Current Topics in Radiation Research, Vol. 6, Eds. Ebert and Howard (North-Holland, Amsterdam), 1970, p. 251.

G. L. Brownell, A. H. Soloway, and W. H. Sweet, Boron-Capture Therapy, in Modern Trends in Radiotherapy, Vol. 1, Eds. T. Deeley, C. A. P. Wood (Appleton-Century-Crofts, New York; Butterworths, London, 1967).

L. H. Gray, Radiobiological Basis of Oxygen as a Modifying Factor in Radiation Therapy, Am. J. Roentgenol. 85, 803 (1961).

H. S. Kaplan, Potentialities of Negative π Mesons in Radiotherapy of Cancer, Los Alamos Scientific Laboratory report LA-4397-MS, 1969, p. 31.

J. F. Fowler, Neutrons in Radiotherapy: Slow Neutrons, Fast Neutrons, and Other Heavy Particles, in Biological Effects of Neutron and Proton Irradiation, Vol. 4 IAEA, Vienna, 1964, p. 185.

B. G. Karlsson, Methadern zur Berechnung und Erzielung Einigenfundie Tiefentherapie Hit Hochenergetischen Protonen Gunstiger Dosisverteilungen, Strahlentherapie 124, 481 (1964).

B. Larsson and B. A. Kihlman, Chromosome Aberrations Following Irradiation with High Energy Protons and Their Secondary Radiation: A Study on dose distribution and biological efficiency using root-tips of Vicia faba and Allium cepa, Int. J. Rad. Biol. 2, 8 (1960).

B. Larsson, Pretherapeutic Physical Experiments with High Energy Protons, Brit. J. Radiol. 34, 143 (1961).

J. H. Lawrence and C. A. Tobias, Heavy Particles in Medicine, Progress in Atomic Medicine, Ed. J. H. Lawrence (Greene and Stratton, New York and London, 1965), p.127.

M. R. Raju, M. Gnanapurani, B. I. Martins, J. Howard, and J. T. Lyman, Measurement of Oxygen Effect and Biological Effectiveness of a 910-MeV Helium Ion Beam Using Cultured Cells (T-1) 1971 (to be published in Radiology).

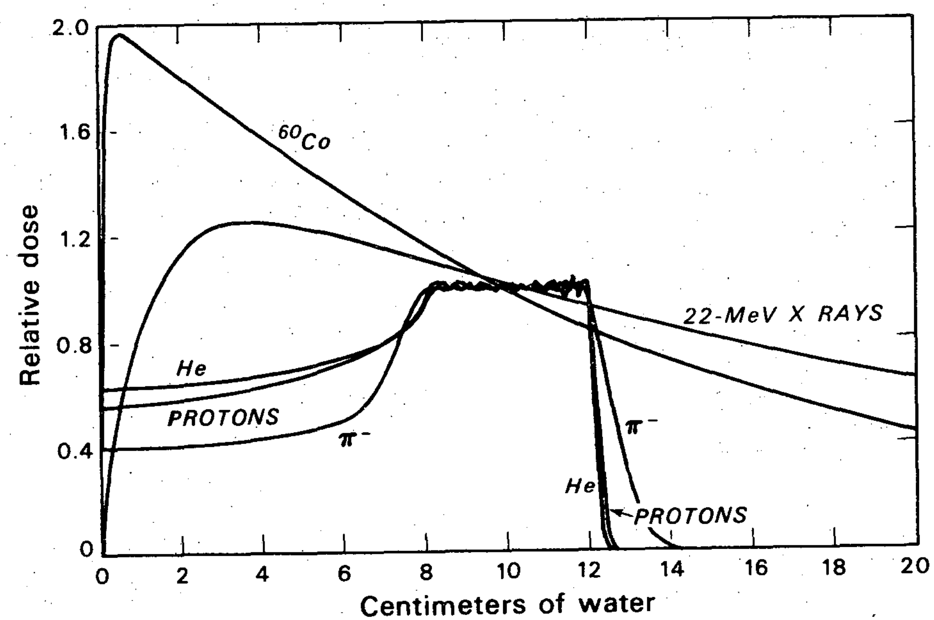
M. R. Raju and C. Richman, Physical and Radiobiological Aspects of Negative Pions with reference to Radiotherapy, in Gann Monograph 9 (Maruzen Co., Ltd., Tokyo, 1970), p. 105.

C. A. Tobias, J. T. Lyman, and J. H. Lawrence, Some Considerations of Physical and Biological Factors in Radiotherapy with High-LET Radiations, in Atomic Medicine, Ed. J. H. Lawrence (Greene and Stratton, New York and London, 1971) (to be published).

R. H. Thomlinson, The Effect of Fractionated Irradiation on the Proportion of Anoxic Cells in an Intact Experimental Tumor, Brit. J. Radiol. 39, 158 (1966).

L. M. Van Putten and R. F. Kallman, Oxygenation Status of a Transplantable Tumor During Fractionated Radiation Therapy, J. Natl. Cancer. Inst. 40, 441 (1968).

H. A. S. Van Den Brenk, The Oxygen Effect in Radiation Therapy, in Current Topics in Radiation Research, Vol. 5, Eds. Ebert and Howard (North-Holland, Amsterdam, 1969), p. 197.



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