TITLE: HEAVY PARTICLE RADIOTHERAPY: PROSPECTS AND PITFALLS

AUTHOR(S): M. R. Raju, LS-1, Toxicology

SUBMITTED TO: Presented at the 1st ARAB Conference on MEDICAL PHYSICS held in AMERICAN UNIVERSITY OF BEIRUT OCT. 30 - NOV. 4, 1980. (PROCEEDINGS TO BE PUBLISHED)
Heavy Particle Radiotherapy: Prospects and Pitfalls
M. R. Raju
Life Sciences Division
Los Alamos Scientific Laboratory

I. INTRODUCTION

I would like to express my appreciation to the organizers of this conference for inviting me to give this special talk. I will attempt to cover the rationale of using heavy particles (protons, helium ions, heavy ions, negative pions and fast neutrons) in radiotherapy, current status, prospects and pitfalls.

The radiotherapist aims to sterilize every tumor cell; however, in practice, the damage to the vital normal tissues located within treatment volume and occasionally outside the treatment volume but within the beam path, restricts the delivery of tumoricidal doses. Hence, sparing normal tissues, by whatever means possible, is a key to success in radiation therapy. The normal tissue tolerance depends on its type, the dose given, and the total volume exposed to radiation. Because of our inability to define precisely the microscopic extensions of the tumor, a large volume of normal tissue suspected to contain tumor cells has to be included in the treatment volume. The normal tissue tolerance decreases rapidly with an increasing volume exposed to the radiation. On the other hand, tumor control increases with increasing dose. The therapist always has to face the perennial problem in trying to deliver maximum dose to increase the tumor control probability without exceeding the normal tissue tolerance so that the morbidity of treatment to the patient is minimum. Clinical results in the treatment of squamous cell carcinoma of the tonsillar fossa indicated that a modest increase of 10 to 20% x-ray dose resulted in 20 to 80% increase in tumor control (Shukovsky and Fletroher 1973). However, the dose response curve does not seem to be that steep for tumor control around and higher than 90%. Also for advanced lesions, the dose response curve was found to be shallow (Thames et al. 1980). Since the reason for using new radiation modalities is to improve the results already obtained with conventional radiotherapy, we are looking for improvements in treating advanced lesions and for early lesions at tumor control rates even better.
than 80%. In order to achieve this goal and see spectacular improvements, these may have to be a >20% increase in the dose to the tumor without exceeding the tolerance of normal tissues. The rationale for using heavy particles is mainly two fold:
1. improvements of dose localization thereby reducing dose to normal tissues outside the treatment volume and
2. if the therapeutic gain (tumor RBE/normal tissue RBE of high LET particles (neutrons, pions and heavy ions) is appreciably greater than unity, then the effective dose to the tumor cells may be increased without increasing the dose to the normal tissues within treatment volume.

II. PHYSICAL ASPECTS

Radiations can be broadly divided into two groups: 1. exponentially attenuating and 2. Bragg ionization characteristics with a well defined range. X rays and fast neutrons belong to the first group and heavy charged particles (protons, heavy ions and pions) belong to the second group. Except for the initial dose build up for high energy x rays and fast neutrons, the dose decreases with depth of penetration. For heavy charged particles on the other hand, the dose deposited increases slowly with depth and then gives rise to a sharp increase in dose near the end of the range due to a Bragg peak effect and there is practically no dose beyond the range of the particle. In addition to the Bragg peak effect near the end of the range, negative pions exhibit a unique phenomenon when they come to rest (Fowler and Perkins 1961). Negative pions (being negatively charged) are captured by atomic nuclei in the medium, and the resulting nucleus disintegrates yielding various particles including some short-range and heavily ionizing fragments. In addition to the Bragg peak effect, this phenomenon increases the dose at depth. The LET at the pion stopping region is also increased because of heavily ionizing fragments. The Bragg peak of nearly monoenergetic heavy charged particles extracted from accelerators is quite narrow and is frequently insufficient to cover the treatment volumes encountered in radiotherapy. The Bragg peak can be broadened by introducing an absorber of variable thickness as illustrated in Fig. 1 for a proton beam. The dose at the Bragg peak decreases with increasing peak width but is never lower than the dose at the entrance. The linear energy transfer (LET) of heavy charged particles at depth especially at the Bragg peak position, is greater than at the entrance.
Fig. 1. Modified depth-dose distribution of a proton beam (Courtesy of Koehler and Preston 1972).
whereas for high energy gamma rays and fast neutrons, there are no significant differences in LET with depth of penetration.

X rays and electrons are often referred to as low-LET radiations, but even these low-LET radiations deposit a small fraction of their dose at LET of about 30 keV/\mu m. The high LET component extends to about 100 keV/\mu m for proton beams, to about 250 keV/\mu m for helium ion beams, to about 900 keV/\mu m for pions and fast neutrons, and for heavy ions is even higher. Thus, the difference between these so-called high-LET radiations is described by the relative proportion of dose in various LET intervals and the maximum LET. All high-LET radiations are really mixtures of various LETs (Raju 1980).

The depth dose distribution of heavy particles of interest to radiotherapy and the range of average LET values of these beams are shown in Fig. 2 and 3 respectively. The depth dose distribution of all heavy charged particles is similar. Among the charged particle beams, the proton beams are least expensive to produce and they have the best dose localization advantage. Protons, however, can be considered as a low LET radiation.

III. RADIobiological phenomena and their modification with LET

The known major radiobiological factors which affect tumor control include recovery from sublethal damage, oxygen effect, variation of radiosensitivity as a function of cell cycle (cell age) and cell proliferation after irradiation. With the possible exception of cell proliferation, the magnitude of changes in response caused by these radiobiological phenomena is reduced when heavy particles are used in radiotherapy.

1. Biological effectiveness and sublethal damage

The biological effect on cells in culture as a function of LET is shown in Fig. 4 (Todd 1964). A typical mammalian cell-survival curve after exposure to low LET radiation has an initial shoulder region, followed by an exponential region. The presence of a shoulder implies that the damage must be accumulated before it becomes lethal. It can be seen that with increasing LET, the shoulder of the survival curve is reduced, and the curve becomes exponential at about 100-200 keV/\mu m. With increasing LET, the cells are killed more efficiently and the $D_0$* value will reach a minimum value at about 100-200 keV/\mu m. With further increase in LET, the survival curve remains exponential but the $D_0$ increases because more energy

* The dose required to reduce cell survival to 37% in the exponential region of the survival curve.
Fig. 2. Measured depth-dose distribution for various heavy particle beams. The distributions were normalized at the peak center (Raju 1980).
Fig. 3A. Schematic representation of the dose average LET values for various heavy charged particles at the plateau and for fast neutrons. (Raju 1980)
Fig. 3B. Dose average LET values in the peak region (Raju 1980).
Fig. 4. Survival curves of human kidney cells for x-rays and heavy ions (Courtesy of Todd 1964).
is deposited in the cells than is necessary to kill the cell. Because of
the changes in shapes of the survival curves of high LET radiations
compared to x rays, the RBE for cell killing depends upon the survival
level at which it is calculated. The RBE is large at low doses (higher
survival levels). Radiotherapy treatments are seldom given in a single
treatment but instead are given as a series of daily treatments (5
days/week) for about 4 to 6 weeks. This protocol was selected because, by
experience, the radiotherapists found that fractionated treatments produce
more effect on tumor cells compared to normal tissues. Elkind and Sutton
(1959) demonstrated that fractionated doses were less effective than single
doses because of the ability of cells to repair sublethal damage between
fractionated treatments. Since the shoulder is reduced with increasing
LET, the magnitude of repair between fractionated treatments will be much
smaller after exposure to high LET radiations compared to x rays. This is
illustrated in Fig. 5 (Hall 1978).

2. The oxygen effect.

The biological effects of low LET radiations are increased by the
presence of free oxygen at the time of irradiation. This enhancement is
known as the "oxygen effect". Enhancement of radiation sensitivity in the
presence of oxygen is commonly expressed as "oxygen enhancement ratio"
(OER) and is defined as the ratio of radiation dose required to produce an
effect under hypoxic conditions to the dose required to produce the same
effect under oxygenated conditions. For x rays, OER ranges between 2.5 and
3.0. The OER decreases with increasing LET (See Fig. 6). The relevance of
oxygen effect in radiotherapy was recognized many years ago. The
radiosensitivity of hypoxic cells in human tumors is overcome at least to a
certain extent due to a phenomena commonly known as "reoxygenation".
Fig. 5. Typical survival curves for mammalian cells for x-rays and for fast neutrons.

A. Single doses.
B. Fractionated doses. (Courtesy of Hall 1978).
Fig. 6. Variations of RBE and OER as a function of LET. RBE curves 1 and 2 correspond to 50 and 20 percent survival levels respectively. Curve "1" represents OER. (Courtesy of Barendsen 1972).
Because of their radiosensitivity, oxygenated cells are killed early in the
course of fractionated treatment, and their decreased respiration and
subsequent loss from tumor permit previously hypoxic tumor cells better
access to the oxygen supply. Thus, cells hypoxic at the beginning of the
fractionated course of treatment become oxygenated thereby becoming
radiosensitive during the course of treatment. The relevance of oxygen
effect in radiotherapy has been discussed for about 50 years, but the
crucial question of whether hypoxic cells are a limiting factor in
fractionated radiotherapy has not yet been completely resolved. It is
quite possible that complete reoxygenation may not take place in some human
tumors. Because of such a possibility, there have been significant efforts
(see Brit. J. Cancer 37, suppl III 1978,) in finding solutions to this
hypothetical problem. The difference in radiation sensitivity between
hypoxic and oxygenated cells increases significantly with high LET
radiations and this is one of the rationales for proposing high-LET
radiations in therapy.


The radiation sensitivity of cells for x rays varies depending upon
the position of cells in the cell cycle. For many cell lines, cells in
metaphase are found to be most sensitive, and cells in late DNA synthetic
phase (late S) are most resistant as illustrated in Fig. 7. The
differences in radiosensitivity during the cell cycle are just as large as
the differences between oxygenated and hypoxic cells. As early as 1914 --
at a time when most therapists were using single doses -- Schwarz advocated
the use of multiple fractions in radiotherapy because multiple fractions
increase the likelihood of irradiating tumor cells when in radiosensitive
stages. Cell cycle variations in radiosensitivity are smaller for high-LET
radiations.

Thus there are large variations in radiation sensitivity of different
tissues for x rays depending upon the ability of cells to repair sublethal
damage, presence of oxygen, and the position in a cell cycle. Some of the
resistance of cells, either because of their position in resistant stages
of the cell cycle or hypoxia, is overcome by using multiple fractions in
radiotherapy. The problem of cell resistance due to hypoxia and resistant
stages in a cell cycle are compounded only if there is a preponderance of
cells in resistant phases among hypoxic tumor cells that are viable. It is
possible that at least part of the resistance of hypoxic cells is
Fig. 7. Cell Survival Curves for Cells in Various Stages of Cell Cycle. The broken line is a hypothetical curve for hypoxic mitotic cells assuming a dose-modifying factor of 2.5 (Courtesy of Smith-Laird 1969).
counterbalanced because of reduction in fraction of cells in late S phase under chronic hypoxic conditions. Since the variations of radiation sensitivity is reduced by using high LET radiations, one can expect to minimize the variability of response from patient to patient. The fact that we are able to treat certain tumors successfully with x rays indicates that tumors can be controlled without exceeding the tolerance limits of normal tissues. The advantages of high LET radiations can easily be demonstrated if the RBE for tumor is higher than the RBE for normal tissues. Such measurements pertinent to human patients at dose fractions used in radiotherapy are not easy, and to date no spectacular increase in tumor tissue RBE for high LET radiations compared to normal tissue has been demonstrated as shown for neutrons in Fig. 8.

IV. FAST NEUTRONS

The first fast neutron therapy clinical trial was performed by Dr. Stone at Berkeley, California during Dec. 1939 - Feb. 1943 ... a period long before the advent of megavoltage radiotherapy and developments of radiobiological techniques. Two hundred and twenty six patients with advanced tumors were treated. After this trial Stone (1948) concluded "neutron therapy as administered by us has resulted in such bad late sequela in proportion to the few good results that it should not be continued." Reduction of the oxygen effect by fast neutrons was unknown at the time Stone conducted his clinical studies. In the light of radiobiological knowledge regarding the oxygen effect in radiotherapy and the reduction in OER for fast neutrons, Gray and his associates in Great Britain felt the need to reinvestigate their use in radiotherapy. After a careful study of fast neutron effects on normal tissues and tumors, patient treatments were started at the Hamman'smith Hospital in 1967. After the initial encouraging results, a randomized clinical trial to compare the clinical results of fast neutrons with megavoltage x or gamma rays was started at Hamman'smith Hospital in 1971. Neutron treatments were given 3 days per week for four weeks. A total dose of 1560 rad of neutrons was given in 12 equal fractions. The tumor regression, relief of pain and ulceration after neutron treatment were found to be significantly better than photon treatments (Catterell et al., 1977). The details of neutron therapy techniques are extensively discussed in a book by Catterell and Dewley (1979). These encouraging results from Hamman'smith Hospital stimulated great interest around the world in the application of fast neutrons in radiotherapy.
Fig. 8. RBE values for rodent tumors and late effects in rodent normal tissues. (Courtesy of Geraci 1979)
A list of neutron therapy centers is presented in Tables I and II. Many of these centers are medically dedicated facilities with isocentric beam delivery capabilities to overcome some of the problems encountered with fixed horizontal neutron beams. A total of about 8000 patients have been treated with neutron beams around the world. The results with brain tumors in general are very discouraging. Good tumor regressions were obtained in general but the advantages of neutrons over megavoltage x-rays is not yet definitely established. The well known problem in comparing the clinical results in different centers is clearly reflected in neutron therapy results in different centers. Neutron therapy is still in the developmental phase and definitive answers will be obtained as more clinical data becomes available after treatment with specially designed hospital-based cyclotrons.

V. PROTONS

The potential application of protons and other heavy charged particles was proposed by Wilson in 1946. Radiobiologically, protons can be considered as a low LET radiation, and thus is simpler to apply the conventional radiotherapy experience to proton radiotherapy. Because of the Bragg peak effect and its sharply defined range, protons offer the potential to confine the high dose region precisely to the tumor volume and to minimize the dose to the surrounding normal tissue. Figures 9 & 10 show dose distributions along one axis for 60Co, 22 MeV x rays and protons. The dose to the normal tissues outside the target volume was about 70% of the tumor dose using 60Co gamma rays. This normal tissue dose was reduced to about 40% when 22 MeV x rays were used and was reduced further to about 22% when protons were used. In addition, the dose was more uniform throughout the target volume, including the edges. The use of a proton beam is almost like extending the skin sparing effect of megavoltage x rays to all normal tissues in the beam path. Computerized tomography is being used for optimizing the treatment planning of proton beams.

The radiotherapeutic application of proton beams has been carried out in Uppsala, Sweden since 1956. As of 1976, about 60 patients had been treated with large fields. The Uppsala Cyclotron is currently being modified and patient treatments are expected within a few years. Prior to 1976, most medical applications of protons at Harvard Cyclotron, U.S.A. were for pituitary treatments of patients with acromegaly, Cushing's disease and chromophobe adenoma. About 1500 patients have been treated; this treatment has become routine and is considered to be the treatment of choice. The cost of such treatments is less than one third that for
Fig. 9. Dose distribution for $^{60}$Co gamma rays, 22 MeV x-rays and protons. (Courtesy of Kocher and Preston 1972)
Fig. 10. Oxygen gain factor [ratio of oxygen enhancement ratio (OER) of x-rays to the OER of the particle] for various particle beams (Raju, 1980).
frontal craniotomy. Large field radiotherapy has been in progress. Proton beams were used either alone or as a boost therapy after conventional radiotherapy. A total of about 250 patients were treated with modest success. The Harvard group has also demonstrated that proton beams may have unique application in treating choroidal melanomas that are currently treated surgically by removing the involved eye. About 36 eyes were treated using proton beams (Cragoudas et al. 1980). The lesions after treatment were found to be either stable or regressing; no retinal complications have been observed, but cataract formation has been seen, as expected, in cases where it was necessary to include a significant portion of the lens within the beam. There is also considerable effort in the U.S.S.R. in proton radiotherapy. Two proton accelerators in the Moscow region, and one near Leningrad are being used. A total of about 500 patients have been treated.

Because of the diversity of clinical material and the lack of randomized clinical trials, the actual benefits of protons in radiotherapy are not very well established. However, the clinical experience indicates that proton beams have potential application in treating tumors of the pituitary, choroid, thyroid, bladder, para-aortic nodes, nasopharynx, prostate, in total nodal irradiation and in pediatric oncology in general.

V. HELIUM IONS

Currently, the 184 in. cyclotron in Berkeley, California is the only facility in use for radiotherapy using helium ions which has nearly all the advantages of dose localization of protons with a modest high LET component in the peak region. This high LET component increases the RBE by about 20% and reduces OER by about 25% compared to conventional radiations.

Helium ion beams have been used also for pituitary treatments. Over 1000 patients have been treated since 1954. Starting in 1975 helium ions have been also used for clinical radiotherapy (Castro et al. 1980). Nonrandomized clinical trials for carcinoma of the esophagus, advanced carcinoma of cervix, ocular melanoma and phase I and II studies for other sites are in progress. A randomized clinical trial for localized unresectable carcinoma of the pancreas is in progress (17 patients with He and 13 patients with conventional radiations), and a clinical trial for esophagus is expected soon. A total of about 250 patients have been treated either with helium ions alone or in combination with conventional radiations or with other heavier ions. The results in general can be considered as a modest success, although no definitive conclusions can be
reached at this stage. The results of choroidal melanoma with helium ions are also found to be very encouraging.

VI. HEAVY IONS.

Two accelerators, a low energy heavy ion linear accelerator and a high energy proton accelerator Bevatron that happened to be located nearby at Lawrence Berkeley Laboratory, were connected with a beam line in 1974. With some modifications in both accelerators, heavy ions such as C, Ne and Ar were accelerated with adequate intensity and range for radiotherapeutic application. This combined facility is known as BEVALAC and to date, this is the only heavy ion facility in the world. However, there are plans to build heavy ion facilities in Canada, Germany, France, Soviet Union and Japan.

Extensive radiobiological studies have been conducted as a preparation for patient treatments. The dose localization characteristics of heavy ions are similar to proton and helium ions but slightly inferior. The LET of these beams especially in the peak region is much higher.

Nearly 50 patients were treated with heavy ions either alone or in combination with either conventional radiations or with helium ions in phase I and phase II studies. These studies will be continued for one more year before phase III randomized studies can be started.

VII. NEGATIVE PIONS

Fowler and Perkins (1961) proposed the application of pion beams for radiotherapy. Pion beams of intensities suitable for radiotherapy became available only recently. Preliminary work on pion dosimetry and radiobiology using low intensity pion beams was done in Berkeley, Geneva and Harwell, U.K.

Three pion beam facilities intended mainly for physics research, but with adequate facilities for therapy have been built at Los Alamos, U.S.A., Vancouver, Canada, and Villigen, Switzerland. The Swiss facility incorporates a pion collecting device developed at Stanford University, U.S.A. This device permits simultaneous multiport irradiation of the tumor volume.

As of April 1980, 145 patients have been treated at Los Alamos. Out of this number, 96 patients received definitive therapy with curative intent. A total pion dose of 4500 rads of pions delivered in 36 fractions over 50 days was adopted for most sites from the experience of phase I and II trials. Although it is too early to make a definitive appraisal, results
of prostatic carcinoma are encouraging but the results of pancreatic carcinoma are not so encouraging. Phase III randomized trial for stages III and IV squamous carcinoma of the oral cavity and pharynx are in progress (Kligerman et al. 1980).

Pilot human studies are in progress in Vancouver, and similar studies are expected soon at Villigen, Switzerland.

VII. COMPARISON AND CONCLUSIONS

If hypoxic cells are a limiting factor, oxygen gain factor (OGF) (the ratio of OER of the x-ray to the OER of the particle beam) is a good measure to compare the efficacy of particles in overcoming the resistance of hypoxic cells. Figure 10 shows such a comparison. Since OER of heavy charged particles depends on the width of the Bragg peak, a range of OGF values corresponding to peak widths of 4 to 10 cm is indicated. The OGF for proton beams is not significantly different from unity; negative pions and carbon ions have similar OGF values and are significantly lower than that for fast neutrons. The OGF values for neon ions are comparable and for argon ions of relatively narrow peak width (say 4 cm) are even higher than those of fast neutrons.

A schematic comparison of heavy particles of interest in radiotherapy, with reference to their dose localization characteristics and possible high-LET advantage, is shown in Fig. 11. Since the biological advantage of high-LET radiations is not yet clinically established, the high-LET advantage is shown with a question mark. The comparative study of heavy particles clearly indicated that there is no unique characteristic in any one particle that is not shared to some degree by other particles. If one is interested in dose localization alone, with no significant alterations in radiation quality compared to conventional radiations, protons are the particles of choice. The question whether high-LET radiation may be more effective for treating resistant tumors could be answered by employing fast neutrons since their dose localization is similar to 60Co gamma rays. Hence, from a scientific point of view, it is necessary to resolve the importance of dose localization using protons and high LET using fast neutrons as an adjunct to the assessment of therapeutic potential of pions and heavy ions. If the clinical results of both protons and neutrons are found to be encouraging, pions and heavy ions will have potential application in radiotherapy. With the increasing costs of energy, the investigations of pions and heavy ions are getting to be quite expensive. Although protons and neutrons were proposed before the use of megavoltage radiations in radiotherapy, systematic clinical investigations got started
Fig. 11. Schematic comparison of different radiations of interest in radiotherapy. The dollar signs ($) represent an approximate cost range (Raju, 1980).
only recently while the improvements in megavoltage radiotherapy maintained a steady phase of development. The dose localization advantage of protons and helium ions was not completely exploited except in pituitary and choroidal melanoma treatments. The pitfall of the particle radiotherapy in general has been that the expectations were too high, and it is quite possible that further improvements in radiotherapy may become apparent in less spectacular ways. Also, the current fractionation schedules used with conventional radiations (five fractions per week for four to eight weeks) may not be optimum for high LET radiations such as fast neutrons and heavy ions. It is known that no further protection to normal tissues from late effects can be obtained by increasing the overall time of treatment say >4 weeks. Although for practical reasons, the conventional fractionation schemes for neutrons and heavy ions may have to be used in the beginning, the optimum overall time for these high LET radiations may be shorter compared to the overall time for conventional radiations.

If hypoxic cells were the only problem that high LET radiation ameliorates, then the advantage of heavy ions and pions can easily be substituted for by combining hypoxic cell sensitizers with protons.

No definitive statement regarding the potential application of heavy particles can be made at this time. In a way it is not surprising since the total experience up to now with all particles does not exceed 12,000 patient treatments compared to about 500,000 patients that receive conventional radiotherapy every year.

A well coordinated, international effort is needed to assess the potential of heavy particles in radiotherapy.
References


Figure Legends

Fig. 1. Modified depth-dose distribution of a proton beam (Courtesy of Koehler and Preston 1972).

Fig. 2. Measured depth-dose distribution for various heavy particle beams. The distributions were normalized at the peak center (Raju 1980).

Fig. 3A. Schematic representation of the dose average LET values for various heavy charged particles at the plateau and for fast neutrons (Raju 1980).

Fig. 3B. Dose average LET values in the peak region (Raju 1980).

Fig. 4. Survival curves of human kidney cells for x-rays and heavy ions (Courtesy of Todd 1964).

Fig. 5. Typical survival curves for mammalian cells, for x-rays and for fast neutrons.
   A. Single doses.
   B. Fractionated doses. (Courtesy of Hall 1978).

Fig. 6. Variations of RBE and OER as a function of LET. RBE curves 1 and 2 correspond to 50 and 20 percent survival levels respectively. Curve "a" represents OER. (Courtesy of Barndes 1972).

Fig. 7. Cell Survival Curves for Cells in Various Stages of Cell Cycle. The broken line is a hypothetical curve for hypoxic mitotic cells assuming a dose-modifying factor of 2.5 (Courtesy of Sinclair 1961).

Fig. 8. RBE values for rodent tumors and late effects in rodent normal tissues. (Courtesy of Gorni 1979).
Fig. 9. Dose distribution for $^{60}$Co gamma rays, 22 MeV x-rays and protons. (Courtesy of Koehler and Preston 1972)

Fig. 10. Oxygen gain factor [ratio of oxygen enhancement ratio (OER) of x-rays to the OER of the particle] for various particle beams (Raju, 1980).

Fig. 11. Schematic comparison of different radiations of interest in radiotherapy. The dollar signs ($) represent an approximate cost range (Raju, 1980).