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J.R. Alonso

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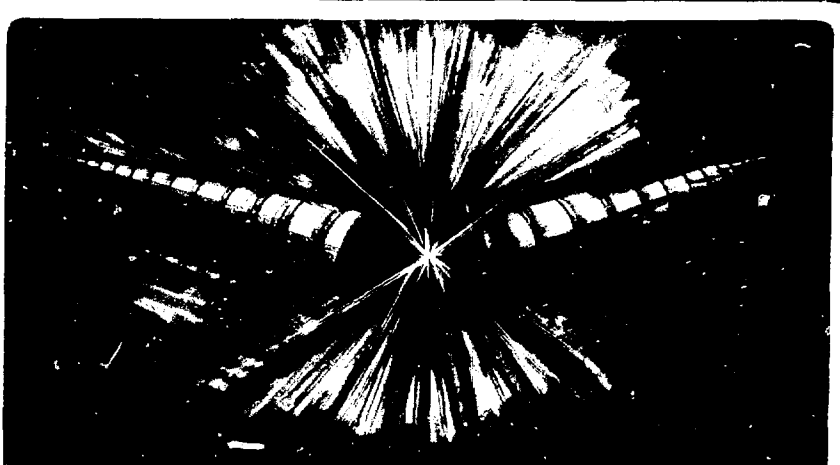

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HADRON PARTICLE THERAPY*

Jose R. Alonso

Lawrence Berkeley Laboratory
University of California
Berkeley, CA 94720

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Jose R. Alonso, Lawrence Berkeley Laboratory, Berkeley, CA 94720

I. INTRODUCTION

Radiation therapy with "hadrons" (protons, neutrons, pions, ions) has accrued a 55-year track record, with by now over 30,000 patients having received treatments with one of these particles. Very good, and in some cases spectacular results are leading to growth in the field in specific well-defined directions. The most noted contributor to success has been the ability to better define and control the radiation field produced with these particles, to increase the dose delivered to the treatment volume while achieving a high degree of sparing of normal tissue. An additional benefit is the highly-ionizing character of certain beams, leading to greater cell-killing potential for tumor lines that have historically been very resistant to radiation treatments.

Until recently these treatments have been delivered in laboratories and research centers whose primary, or original mission was physics research. With maturity in the field has come both the desire to provide beam facilities more accessible to the clinical setting of a hospital, as well as achieving highly-efficient, reliable and economical accelerator and beam-delivery systems that can make maximum advantage of the physical characteristics of these particle beams. Considerable work in technology development is now leading to the implementation of many of these ideas, and a new generation of clinically-oriented facilities is beginning to appear.

We will discuss both the physical, clinical and technological considerations that are driving these designs, as well as highlighting specific examples of new facilities that are either now treating patients or that will be doing so in the near future.

II. HISTORICAL DEVELOPMENTS[1]

A. *Fast Neutron Therapy*

Being neutral, and hence not interacting electromagnetically with matter, fast neutrons impart their energy to matter through nuclear reactions. It is the recoils from elastic collisions, and nuclear disintegration products that contribute to the dose to biological tissue. Depth dose distribution for 30 MeV neutrons resemble the spectrum of an 8 MeV photon beam, with an exponential falloff (50% attenuation in about 15 cm of water). The character of the radiation, however, because of the low energy of the recoiling particles, is said to be "high LET" (Linear Energy Transfer, a measure of the energy deposited in tissue by the particle). The high ionization density creates more severe local destruction to biologically-active molecules.

E.O. Lawrence always had a great interest in finding medical applications for his cyclotrons, and early work on the production and biological characterization of fast neutrons led, in 1938 to the initiation of a treatment program. A total of 226 patients were treated with neutrons produced from the 30" and 60" cyclotrons between 1938 and 1941. The treatments were interrupted by WW II, but an analysis of the outcome of this treatment program, performed after the war, revealed that although early response was not bad, the high-LET late effects, in the form of complications to normal tissue and organs, were extremely severe. These observations led the medical researchers to conclude that the program should not be continued until further studies of early and late effects could be performed [2].

In fact, it was not until 1970 that the resistance in the medical community was overcome sufficiently that a program was started at the Hammersmith Hospital in London, using a 60 MeV cyclotron. Careful work by Mary Catterall and her co-workers [3] yielded some of the answers that had eluded the earlier researchers, and formed the basis for a substantial program of treatment with fast neutrons. Today, eight centers in Europe, five in the US, five in Japan and Korea, and one in South Africa are treating patients using cyclotrons, D-T generators and linacs [4]. Neutrons are produced by 30 to 70 MeV protons striking a beryllium target, or 14 to 50 MeV deuterons on beryllium, or in the case of the D-T generators, 14 MeV neutrons come from 200 keV deuterons striking the tritiated target.

Current results from these programs clearly indicate that certain classes of patients can benefit by the use of fast neutrons [4]. Salivary gland and paranasal sinus tumors are controlled much better than with photons, and promising results were obtained in some other sites, for example soft tissue sarcomas and prostatic adenocarcinomas. Late effects now seem to be better understood, and carefully-crafted treatment plans can minimize the deleterious effects.

B. *BNCT (Boron Neutron Capture Therapy)[5]*

The principle is quite simple: attach a nucleus with a high thermal-neutron capture cross section to a pharmaceutical that is preferentially absorbed by tumor tissue, then flood the area with thermal neutrons. The increased number of nuclear disintegrations in the tumor provides the dose concentration that will produce an improved clinical effect. This idea was first proposed in 1935 [6,7], and a clinical program treating brain tumors was undertaken at reactors at MIT and Brookhaven between 1951 and 1961. This program was not successful, mainly because the hoped-for increase in dose to the tumor could not be obtained due to poor uptake ratio of the pharmaceutical and the non-optimal spectral distribution of the neutrons [8]. This concept, too, lapsed into disfavor and was not resurrected until 1970 when a Japanese group [9] reported very promising results using a new class of drugs, and an intra-operative procedure to directly expose the tumor to the thermal neutrons. Considerable activity is now taking

place in this field, with new families of pharmaceuticals promising even higher tumor-uptake ratios, and tailoring of neutron spectra, starting with epithermal neutrons, and using brain tissue itself to moderate the neutrons to the desired thermal spectrum at the site of the (deep-seated) tumor[10]. BNCT is being eyed with much hope as an effective treatment for gliomas, tumors that have been notoriously resistant to any other form of therapy.

C. *Protons*

Protons were recognized by Bob Wilson in 1947[11] as having excellent potential for radiation therapy due to the 1/E nature of the energy-loss process. As the proton slows down it loses proportionately more energy, the greatest energy-deposition in the medium occurring just as the particle stops (the so-called "Bragg Peak"). By adjusting the proton energy so it will penetrate to and stop in a tumor, most of the radiation damage is done in the tumor itself, while the normal tissue traversed on the way to the tumor is largely spared. The comparative rigidity of the proton allows it to travel in an almost straight path to its stopping point, providing for good localization of the dose. Multiple scattering and range straggling will broaden the stopping point somewhat, but at depths of 15 to 20 cm, dose-falloffs of 8 to 10 mm are possible. Shallower depths are proportionately better. Note that proton therapy is considered as a "low-LET" modality, the ionization density for the stopping proton beam is comparable with that of a photon beam.

The first use of protons in therapy was performed at the Berkeley 184" Synchrocyclotron[12] in 1952, for pituitary treatments. Rotational therapy (twisting the head about the pituitary as a center of rotation) was used with a high-energy beam, not trying to stop the beam because of uncertainty in the tissue-thickness on the way to the target. The first Bragg-Peak therapy was performed at Uppsala in 1956[13] using their 230 MeV Synchrocyclotron. Noteworthy programs in Russia[14] and Japan[15] also pioneered many of the techniques for using protons in therapy. In 1965 the 170 MeV Synchrocyclotron at Harvard was converted from its nuclear physics use into a dedicated medical facility, and became the site for the longest-running and very successful program in radiosurgery and therapy with protons [16,17]. Extremely high success rates were obtained with ocular melanomas, and chordomas and chondrosarcomas, tumors very close to critical structures (optic nerve and spinal chord, respectively). For successful treatment beam had to be placed with millimeter accuracy to prevent unacceptable complications. These treatments were possible because of the sharp stopping of protons in these relatively shallow target volumes. To date over 16,000 patients have been treated at these and other, newer facilities, with good indications of success in a wide range of tumors. Of all the hadron modalities, protons are the most widely accepted today, and significant growth is occurring with many proton therapy facilities in planning and construction[18].

D. *Pions*

Fermi recognized the possible use of pi-minus mesons in medicine; formal proposal of their use for radiation therapy was made by Peter Fowler in 1961[19]. The pion exhibits the same Bragg curve stopping behavior as the proton (although being lighter does suffer more from multiple scattering), but the π- is captured as it stops causing the capturing nucleus to disintegrate, adding a "star dose" of high-LET radiation to the Bragg Peak. Early characterization and dosimetry work was done at Berkeley (184") and CERN (SC), but it was not until the meson factories at Los Alamos, PSI and TRIUMF were built that sufficient flux was available to contemplate a medical therapy program. Programs were conducted at all three[20,21,22] and over the last 20 years 1000 patients have received pion treatments. Noteworthy is the "Piotron"[22] built at PSI from an idea proposed by Kaplan at Stanford years earlier[23]. To increase the dose rate, this "pion concentrator" consisted of a 60-channel "orange-peel" type spectrometer, collecting pions from a conical section 60° from the beam axis and bringing 60 beamlets to an image-point of the target. A positioner brought the patient to this point, and moved the patient around so all points in the treatment volume were exposed to this concentrated spot.

On the whole, the clinical results from these programs were good, but not outstanding. The general consensus of the researchers is that while pions are effective, they do not seem to show clinical results that are much better than other hadron beams. Considering the size and expense of machines needed to produce high fluxes of pions, it is unlikely that a practical, cost-effective hospital-based pion therapy facility will ever be built. The TRIUMF program, the last of the three still in operation, will stop accruing patients in 1995.

E. *Heavy Ions (C, Ne, ...Si)*

With the commissioning in 1974 of the Bevalac in Berkeley, the use of ions heavier than protons for therapy became a possibility. In fact, funding for the transfer line between the SuperHILAC and the Bevatron, critical link in the creation of this composite machine, was provided by life-sciences with the object of investigating the potential of heavy ions for medical applications. To achieve the necessary 30 cm range in tissue requires energies of 400 MeV/amu for carbon or 600 MeV/amu for neon ions, energies not available before the Bevalac came into being.

These ions are heavier than protons, will scatter less and so provide sharper edge-definition for the radiation field. On the other hand, the nuclear mean-free-path is comparable to the treatment depth so that a significant amount of the beam can be lost to nuclear reactions, mostly peripheral transfer reactions, producing light fragments that travel beyond the stopping point of the primary beam. This "tail dose" becomes appreciable for heavier ions at depths greater than about 20 cm.

Since ionization density varies as the square of the ion

charge, heavy ions have higher LET than protons. Based on a fairly arbitrary threshold, it is argued that the slowing-down region (called the "plateau") for carbon ions is "low-LET" while the "peak" is higher LET, offering the best advantage of normal-tissue sparing and good tumor-killing. On the other hand, researchers at LBL observed that neon ions would provide a better test of high-LET effects, and in fact this is the ion primarily used in the Bevalac program. Note that heavier ions than neon will exhibit very high ionization in the slowing region, and an "overkill" in the stopping region, so were not considered for any but the most superficial of tumors, in which little or no normal tissue would have to be traversed. A few such tumors were treated with silicon and argon beams.

Between 1974 and 1993, the year the Bevalac closed, over 400 patients were treated with these ions. Many different tumor types were treated, to get an overall view of the benefits that might be obtained. Castro, the lead physician in this program, reports promising results[24] in many sites, but particularly for advanced prostate carcinomas, as well as soft-tissue osteo-sarcomas, tumors that are normally very resistant to radiation treatments. However, statistics are low, and it is clear that more experience is necessary before the overall clinical utility of heavy ions can be established. Results have been encouraging enough, though, that two major efforts have been launched to continue the trials begun at the Bevalac. The HIMAC facility in Chiba, Japan is now treating patients, and a program at GSI in Darmstadt, Germany, is preparing a medical area and will begin treating patients in about two years. Both of these programs will be described further later in this paper.

III. LESSONS LEARNED

A. *Dose Localization*

Tumor control is significantly improved when the dose can be more precisely placed. Spectacular improvements in cure rates have resulted from the advent of CT and MRI diagnostic devices that have for the first time allowed accurate definition of target volume. Radiation therapy is still lagging in its ability to place the desired radiation dose into the optimally-defined target volume. Dose concentration with photons is obtained by multi-port treatments, irradiating the patient from different angles with the beams overlapping in the tumor region. The current generation of compact linacs used for x-ray therapy are installed on a gantry so can be easily rotated in a vertical plane about the patient lying on a table at the center of the beam arc. The overlap region, however, cannot without great difficulty be made to conform to the irregular shape of the tumor volume, so a significant amount of normal tissue is exposed to a higher-than-desired dose.

The Bragg Peak and the ability, in principle, to place stopping particles in any coordinate of the body gives ions a natural advantage over photons to improve further the selectivity and precision of radiation therapy. The juxtaspinal (i.e. chordoma) treatments are a case in point. In many cases the tumor surrounds the spinal chord, so the desired treatment volume would be a toroid. By controlling the stopping point to come short of entering the chord, ions can deliver a treatment that keeps dose to the chord to an acceptable level. Such a treatment is essentially impossible with photons.

In practice, even with ions, treating an arbitrarily-shaped volume without involving normal tissue in the high-dose field is technologically very complex, in fact no patients have been treated yet with such a fully "three-dimensional" system. Typically the maximum outline of the treatment volume is defined by a shaped collimator, the maximum penetration is contoured by a "bolus compensator" placed in front of the patient, then the range is modulated by a ridge-filter that spreads stopping particles over the maximum thickness of the tumor. This "delta-Z" is the same for all parts of the field, defining a cylindrical section of uniform high dose. The normal tissue in this cylinder outside the tumor volume receives the same dose as the tumor.

In fact, technology does exist to overcome this limitation, but it is very complex and requires much development and testing prior to being mature enough to use with actual patients. In addition, the implementation of such scanning systems place many constraints on the accelerator performance, requirements often not found in conventional accelerator designs. These will be discussed below.

B. *High LET*

Heavy-ion and neutron treatment results do show that high LET can kill tumors that have resisted other forms of treatment. Normal tissue is also damaged more by these particles, and in particular side effects can show up many months after the treatment has been completed. Maximum effectiveness then requires an extremely delicate balance, and also the need to keep to an absolute minimum the involvement of normal tissue in the high-LET radiation field. Again, this requires the most sophisticated delivery systems. Defining this balance in the treatment plan requires the greatest possible knowledge of the response of both normal and tumor tissues to the radiation in question; much of this information is not available now.

Much more research is required to optimize the use of high-LET radiation, but the potential benefits for patients with difficult tumors could be very high. Adding to the complexity is the extra degree of freedom in the mass (or charge) of the ion that is used. On the other hand, this flexibility can add further to the benefits available from a finely-tuned treatment plan customized for each patient. A technique, called "predictive assays"[25] can assist in selecting the appropriate treatment: samples of tumor and normal tissue are taken from the patient and are exposed to different radiations to determine the response of these particular cell types. The treatment plan, and even the best ion to use, can be selected by this means.

IV. DESIGNING FOR OPTIMUM EFFECTIVENESS

The best conformation of the radiation dose to the clinically-defined target volume can be achieved if careful attention is paid to the design of the accelerator and beam-delivery systems. Paramount for proton and ion therapy is the preservation of beam quality to prevent loss of sharpness due to range straggling and multiple scattering. Range variations should take place by adjusting the energy of the beam outside the treatment room, not by degraders; and lateral spreading should use magnetic deflection rather than scattering systems. Precise three-dimensional dose deposition requires very fine control over the instantaneous beam current, and the ability to quickly adjust the coordinates (x,y,z) of the stopping beam with high accuracy. Considering that a typical target volume may be subdivided into 10^6 volume elements that must be independently irradiated to a ±2% dose accuracy in less than 2 minutes, the complexity of the delivery system becomes apparent. A close coupling of the accelerator performance and the delivery system is the only way of assuring success. Performance specifications for the accelerator have been carefully studied, and although quite stringent, do fall within today's state of the art[26].

The ease of treatment afforded by placement of photon sources on a gantry has indicated that all modern treatment facilities should have this capability. Treating in the supine position not only adds to patient comfort, but is critical for use of the essential diagnostic information from CT and MRI scanners. Proton gantries are large, in many cases larger than the accelerator, but nonetheless feasible. A heavy-ion gantry is unmanageable with today's technology, but fixed beams at different orientations can come close to providing the necessary flexibility.

V. NEW FACILITIES

A. *Fast Neutrons*

The state-of-the-art neutron therapy facility is embodied in the gantry-mounted superconducting deuteron cyclotron[27] built by Henry Blosser for the Harper Hospital in Detroit. The 48.5 MeV, 15 μA deuteron beam strikes an internal beryllium target producing a neutron dose rate of 40 cGy/min. As the whole cyclotron rotates around the patient there is no need to extract the beam from the cyclotron, nor for any beam-transport system. In full use since early 1992, about 150 patients per year are now treated.

B. *BNCT*

If the clinical advantages of BNCT are demonstrated, a hospital-based program will most likely be implemented with accelerator technology rather than with reactors. Neutrons are produced by protons striking lithium or beryllium targets, the epithermal spectrum is obtained with a suitably-designed moderator. To treat a patient in a reasonable time (less than one hour) the p-Li reaction will require a proton beam current between 10 and 100 mA (average) at 2.5 MeV, the p-Be requires somewhat less current (5-10 mA) at around 20 MeV. High duty-factor RFQs and electrostatic generators are being developed for the lower energy application, while high-current cyclotrons might meet the need for the higher energy. R&D is progressing, and these systems should be ready for patient treatments in a few years.

C. *Protons*

The first hospital-based proton facility at Loma Linda has been operational since 1990, and has treated over 1000 patients[28]. A 250 MeV (weak-focusing) synchrotron delivers beams to three gantry rooms and two fixed-beam rooms. Although not now using advanced delivery systems, the flexibility of the accelerator allows for their implementation when it is felt the technology is suitably tested for reliable use with patients. The accelerator and ancillary technical systems have demonstrated extremely high reliability, and stand as a demonstration of the readiness for introducing complex accelerator systems into hospital settings.

The Paul Scherrer Institute in Switzerland is now commissioning a compact gantry system with a line-scanning system that will be capable of treating 3-dimensional volumes[29]. Attached to the high-current, 600 MeV cyclotron, this proton-therapy facility uses only a tiny fraction of the available beam, degrades it to 200 MeV, followed by cleanup by collimation and momentum-selection prior to entering the gantry system. Patient treatments are expected to start this summer.

Construction is well underway for a new facility at the Massachusetts General Hospital in Boston. A 235 MeV cyclotron will deliver beam to one gantry and one fixed-beam room. Energy variation is obtained by degrading the beam followed by collimation and momentum selection. The compact cyclotron is being built by IBA (Belgium), field mapping starts in June 1995. Patients treatments should start in 1998.

About ten other facilities are in operation today, many of them low-energy (≈70 MeV) cyclotrons dedicated to eye treatments. Several projects are in various planning stages, in Texas, Italy, Russia and Japan[13].

D. *Heavy Ions*

The HIMAC facility in Chiba, Japan stands as the premier facility dedicated to hadron therapy today. This large complex consists of two 800 Mev/amu synchrotrons one above the other, injected by a 6 MeV/amu Alvarez linac[30]. Ions from helium to silicon can be delivered to one of three treatment rooms, equipped with horizontal and vertical beam ports. For accurate patient positioning, a CT scanner has been installed in each treatment room. As described earlier in these proceedings[31], this facility has now completed its commissioning, and since October 1994 has treated 21 patients with carbon beams. The beam-delivery system is closely patterned after that used for many years at the Bevalac, a two-dimensional system based on wobbler magnets[32], but

it is anticipated that a more advanced system will be implemented in future years.

GSI, in Darmstadt, is beginning serious work on a patient treatment facility. Clearly defined as a technology demonstration effort, rather than an outright clinical program, new and innovative techniques are being developed and will be tested with patients[33]. Pulse-to-pulse energy variation has been demonstrated from the SIS synchrotron, and a scanning system is now operational that has demonstrated spectacular abilities in painting beam into complex shapes. Excellent conformation to defined target volumes should be achieved. In addition a technique, first developed in Berkeley[34] for using positron emission from radioactive ions to localize the stopping point of the treatment beam is being implemented. Patient treatments are expected to start in 1997.

Planning for other heavy-ion facilities is progressing as well: the AUSTRON project in Austria will consist of a carbon synchrotron built in conjunction with a spallation neutron source, the TERA project in Milan plans initially for a proton synchrotron that can be upgraded to carbon capability with addition of a new injector, and the Hyogo Prefecture will build a carbon-ion treatment facility close to the SPRING-8 site. Start of this last project has been slightly delayed by the recent Kyoto earthquake, but the determination to proceed with the project has not been affected.

VI. SUMMARY

Hadron therapy is a maturing field, with strengths and weaknesses that have been clearly identified. For certain tumor types, particles have become the treatment of choice, and hospital-based implementation of these techniques are coming on line. Focused R&D programs in critical areas of beam-delivery, treatment planning and radiobiology are underway at many centers around the world, increasing the scientific and technological base needed to best utilize these modalities.

Cancer is a highly complex disease; effective control requires a wide arsenal of treatment techniques. The flexibility and precision of hadron therapy are powerful tools in this arena, and promise to provide great improvements in our health-care when fully understood and implemented.

VII. REFERENCES

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