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Light-Ion Therapy in the US: From the Bevalac to ??

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Introduction

While working with E.O. Lawrence at Berkeley, R.R. Wilson in 1946 noted the potential for using the Bragg-peak of protons (or heavier ions) for radiation therapy[1]. Thus began the long history of contributions from Berkeley to this field. Pioneering work by C.A. Tobias et al[2] at the 184-Inch Synchrocyclotron led ultimately to clinical applications of proton and helium beams, with over 1000 patients treated through 1974 with high-energy plateau radiation; placing the treatment volume (mostly pituitary fields) at the rotational center of a sophisticated patient positioner[3]. In 1974 the SuperHILAC and Bevatron accelerators at the Lawrence Berkeley Laboratory were joined by the construction of a 250-meter transfer line, forming the Bevalac (see Figure 1), a facility capable of accelerating ions of any atomic species to relativistic energies[4]. With the advent of these new beams, and better diagnostic tools capable of more precise definition of tumor volume and determination of the stopping point of charged-particle beams, large-field Bragg-peak therapy with ion beams became a real possibility. A dedicated Biomedical experimental area was developed, ultimately consisting of three distinct irradiation stations; two dedicated to therapy and one to radiobiology and biophysics. (Figure 2). These facilities included dedicated support areas for patient setup and staging of animal and cell samples, and a central control area linked to the main Bevatron control room.

Figure 1: The Transfer Line (dotted line) brought the heavy-ion capabilities of the SuperHILAC (top) to the Bevatron, forming the Bevalac, the world's first relativistic heavy-ion accelerator.

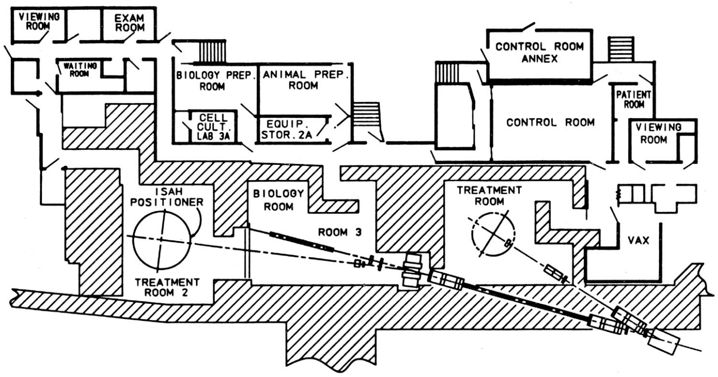

Figure 2: Biomedical experimental area at the Bevalac, showing two therapy rooms and a biology/biophysics area. ISAH, the patient positioner used at the 184-Inch was moved to the Bevalac upon closure in 1985 of the 184.

Bevalac Program

Clinical experience

In 1975 a series of Phase I/II trials was initiated in a joint program between the Lawrence Berkeley Laboratory and the University of California, San Francisco Medical Center, led by Dr. Joseph R. Castro, utilizing both the 184-Inch and the Bevalac. Over the following eighteen years, around 1200 patients were treated at these two facilities; 433 patients receiving irradiations at the Bevalac with beams of helium, carbon, neon, silicon and argon. The 184-Inch patients received treatments with helium beams. The majority of Bevalac patients were treated with neon. About half of these patients received boost fractions, the remainder were treated exclusively with neon beams. Sites treated focused on skull-base tumors, where the superior dose-localization capabilities enabled dose delivery in close proximity to critical normal structures; and on various radioresistant tumor types, where

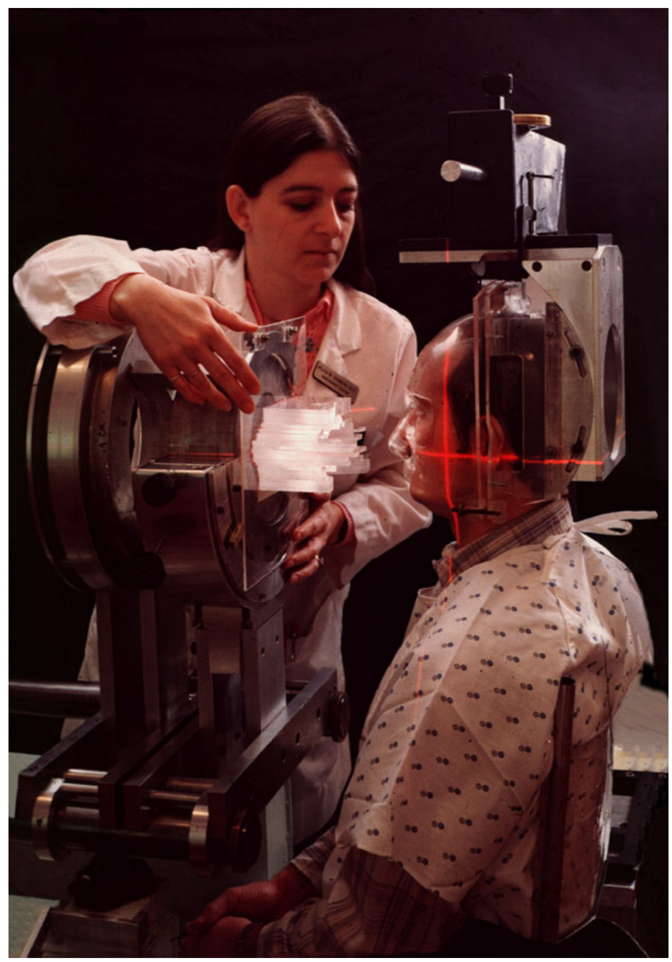

Figure 3: Seated patient treated with horizontal beam (from left). Plexiglass bolus compensator adjusts distal edge of treatment field. Cerrobend collimator shapes the trasnverse field dimensions. Immobilization provided by head mask.

the high LET of light-ion beams was expected to show clinical improvements over conventional treatment. Results confirmed expectations of superiority in both dose localization and biological effectiveness of high-LET beams[5]. Clinical results from these trials are summarized in the paper of P. Pommier later in this session[6].

Beam delivery techniques

Beam rigidity for the 670 MeV/amu neon beam used was such that it was not possible at the Bevalac to provide anything but a static horizontal beam for treatment. Achieving different port orientations required rotating the patient around the beam, instead of the conventional technique of placing the patient at isocenter and rotating the beam around the target. Most of the treatments were performed with the patient seated, with a chair interfaced to a standard therapy couch. (Figure 3) The program benefited greatly by the acquisition of a special CT scanner, a modified EMI-7070 with either horizontal or vertical scan planes, which was capable of scanning the patient in either supine or seated treatment position. This unit was indispensable for development of treatment plans accurately depicting patient geometry.

Shaping the beams to conform to a desired irregular target volume presented significant challenges. Large, uniform fields were initially obtained using double-scattering, developed at the 184-Inch[7] and the Harvard Cyclotron Laboratory[8]. Fields up to 25 cm diameter were obtained, with flatness of about ± 3%. The lateral dimensions of the field were defined by custom-made cerrobend collimators. Bragg-peak modulation was performed with ridge filters, producing spread-out Bragg peaks of the same fixed width over the entire field. The distal edge of the Bragg peak was adjusted using a water-column range shifter, and spatial variation of this edge provided by custom-made bolus compensators made from cast wax or machined plastic.[9] While these techniques provided a good initial solution for protons and helium ions, the application of the double-scattering technique to light-ion beams produced substantial degradation of the beam quality. Because of the high-energy and rigidity of the beams, scattering thicknesses of the order of a full cm of lead were needed, causing excessive loss of beam range, but more important was the conversion of a significant fraction (almost 50%) of the beam, through nuclear reactions, into lighter fragments, diluting the high-LET characteristics of the beam, and providing a significant dose beyond the stopping point of the primary beam.

To overcome this problem, the Wobbler beam delivery system was developed.[10] It consisted of a pair of electromagnets with fields oriented at orthogonal angles and driven sinusoidally at ≈ 60 Hz, sweeping the beam in circular patterns. (See Figure 4.) Adjusting the amplitude of the sine wave allowed for painting circles of different diameters, so that a full field up to 30 cm could be produced by superposing several concentric circles with different radii. This significantly reduced the amount of material in the beam, thus improving beam quality. It added quite a bit of complexity to the control system for beam delivery, and placed more stringent requirements on the stability of the beam extracted from the Bevatron. The Wobbler system was used for clinical treatments for approximately the last six years of the Bevalac program.

Figure 4: Wobbler magnets – 1-meter long dipoles with sinusoidally-driven fields that produce circular beam patterns at patient site, 5 meters downstream (towards lower-right). Field sizes of ± 2% uniformity, up to 30 cm diameter could be obtained by overlapping several circles of different radii.

The treatment fields, even with the Wobbler, were "2-dimensional," that is the modulation of the spread out Bragg peak was constant over the full transverse field, so normal tissue was by necessity included in the 100% dose volume. Two techniques were developed for conforming the treatment field more closely to an arbitrary 3-dimensional shape, thus sparing the maximum amount of normal tissue: a) the Variable-Modulation scheme and, b) the Raster Scanning system.

In the Variable-Modulation technique a narrow SOBP (Spread-Out Bragg Peak) is conformed to the distal edge of the field, distally shaped with a bolus compensator. The transverse shape is set by a multi-leaf collimator. When the desired dose is given to this slice, the range of the beam is reduced, and the transverse shape is adjusted by changing the leaf positions, to treat the next shallower slice. This process is repeated until the whole volume is treated. A multi-leaf collimator was developed, and test runs were performed with it to demonstrate the viability of the Variable-Modulation technique; however the full system was not commissioned and put into routine service before the Bevalac program ended.

This technique has now been fully implemented at HIMAC, in Chiba, Japan, and is the primary means utilized at this facility for achieving 3-dimensional field shapes[11].

The Raster Scanning system, like the Wobbler, uses two orthogonal electromagnets, but adjusts the sweeping algorithm of the beam in a more controlled fashion. In its simplest implementation, a rectangular pattern is employed, much like the sweep of a cathode ray tube. A pair of Raster Scan magnets was fabricated and installed at the Bevalac, just prior to the cessation of operations[12]. (See Figure 5.) Field-definition techniques adapted from those used with the Wobbler were employed. Several fractions of a patient's treatment were delivered utilizing this system, to officially declare the system operational.

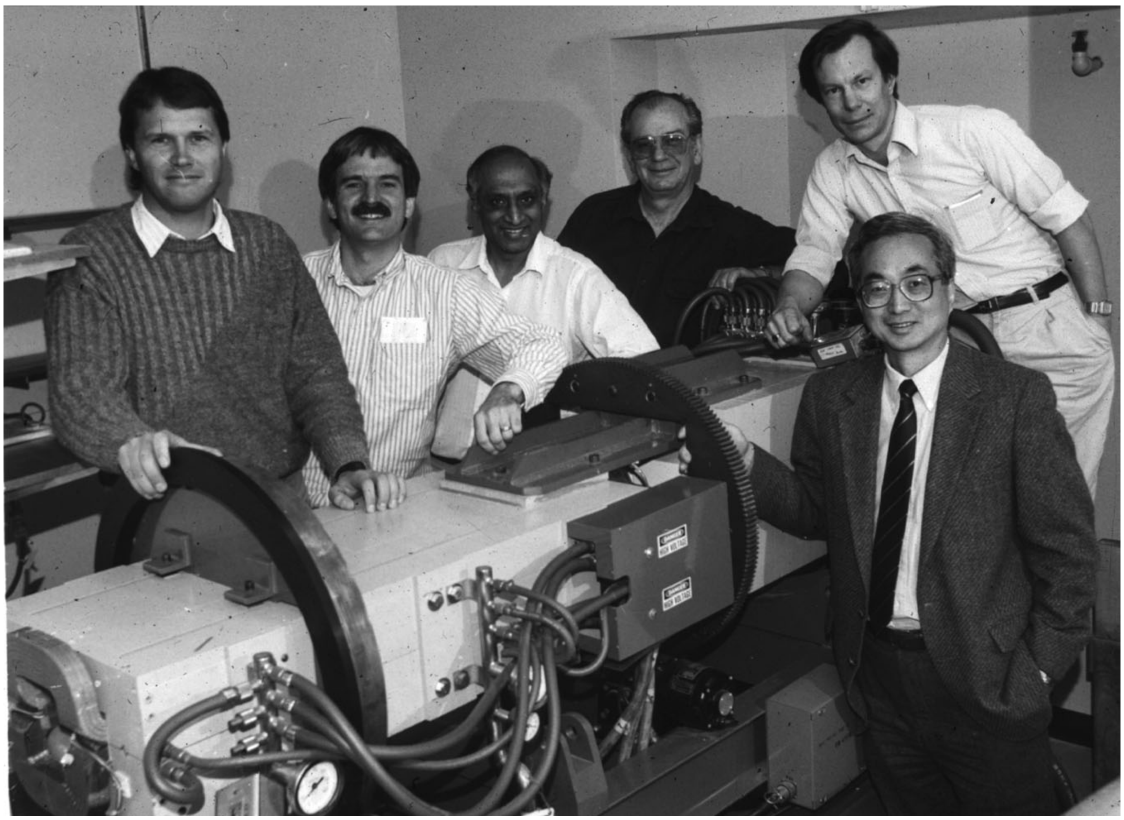

Figure 5: Bevalac Raster Scan magnets installed in Biomed area, with physics, engineering Bevalac operations team. Left to right: B. Ludewigt, T. Renner, R.P. Singh, R. Stradtner, M. Nyman, W. Chu.

In a more sophisticated application of raster scanning, a small (≈ 5 mm dia) beam spot is kept at a spot (x,y,z) until the desired dose is delivered, then the scanner is commanded to move to the next (x,y) coordinates. When a full depth (z) plane is finished the beam energy is adjusted, and the scanner is reset to sweep over the target coordinates of the next shallower plane. This truly "3-dimensional" technique, which represents probably the most flexible and accurate beam-delivery technique available for charged particles, was discussed at length by physicists and engineers at Berkeley, but never developed primarily because of limitations of the Bevatron to accommodate the rapid and accurate changes in extraction necessitated. It has been successfully applied now at GSI[13], with considerable success.

Radioactive beams

The use of radioactive beams was also pioneered at the Bevalac[14]. Grazing collisions of nuclei are capable of stripping one or more nucleons from the projectile with little change in the velocity of the projectile. This process is highly efficient, so that as much as 1% of a ^{20}Ne beam could be converted to ^{19}Ne, purified and transported successfully into the treatment area for diagnostic use via PET imaging. The stopping point of the beam could be measured with precision of about 1 mm, to verify the accuracy of the treatment plan. This technique was successfully applied with a number of neon patients with fields in complex anatomical regions.

End of the Bevalac program

The Bevalac ceased operations in 1993, when the U.S. Department of Energy's Nuclear Physics program withdrew operations funding. New nuclear-physics facilities in the US, at Brookhaven National Laboratory (the Relativistic Heavy Ion Collider – RHIC), and the Continuous Electron Beam Accelerator Facility – CEBAF at Newport News, VA were coming on line, and to support their operations, it was necessary to close older facilities. For the preceding 15 years, the entire operations of the Bevalac had been paid from the Nuclear Physics budget of the US Department of Energy, even though by agreement from the beginning of Bevalac operations, one-third of the time was to be dedicated to biomedical research. Thus, withdrawal of Nuclear Physics funding reduced to zero the amount available to keep the Bevalac operating. This was most unfortunate, particularly since the therapy program had just secured funding for another five years with an extremely high priority score. The Department of Energy offered exclusive use of the Bevalac for the therapy program, but while the National Cancer Institute wished to fund the treatment program itself, it was unwilling to assume responsibility for the funding necessary to keep the Bevalac running.

Lessons learned from Bevalac experience

Looking back on the Bevalac years, and assessing the experience gained, several very important conclusions can be drawn.

Clinical use of light-ion beams is clearly feasible, and definitely worth pursuing

Even from the relatively small number of patients treated, clinical results showed statistically significant improvements in tumor response, reductions in normal tissue complications, and improvements in overall survival rate of the patients treated. Results certainly justifying continuation of experiments with these beams, to further develop and optimize the modality. If the relatively crude beam delivery techniques available with the Bevalac could show these results, it should be anticipated that even better results could be obtained with more refined techniques developed from experience gained at the Bevalac.

Most effective utilization of light-ion beams requires very sophisticated beam-delivery technology

Use of ion beams, heavier than protons, clearly requires active magnetic deflection systems to treat field sizes larger than a few cm^2. Such systems introduce a high degree of complexity in the instrumentation, control and accelerator systems. Fast, highly accurate and reliable beam monitoring devices are required, generating large streams of data that must be analyzed to make decisions about control of magnet currents and accelerator parameters on time scales of microseconds. Precision in response of these accelerator and magnet systems must be extremely high. Validation of control system software and hardware to ensure safe and reliable treatments is of critical importance, and is a formidable task. Formidable, however quite achievable, but not to be underestimated. It requires substantial investments of talent, time and resources.

Sharing a major nuclear-physics research facility with a clinical program is very difficult, and should be avoided if at all possible

The Bevalac, the world's first high-energy heavy-ion facility, initiated research in a number of new fields. High-energy collisions in systems as heavy as uranium-on-uranium opened up the study of the equation of state of nuclear matter. Atomic physics with hydrogen-like uranium could only be done with beams of Bevalac energies. Space-sciences discovered that the Bevalac could produce a ground-based source closely simulating the galactic cosmic ray spectrum in both ion species and energy distribution. All this in addition to the clinical program, and the accompanying radiobiology and biophysics programs with light- and heavy-ion beams. Many communities wished access to the Bevalac, and unfortunately the experimental requirements of these communities were often incompatible.

Specifically, the therapy program required access to beam several hours per day for four or five days per week to deliver fractionated treatments. Most of the other programs required long blocks of dedicated time, and could not tolerate interruptions for patient treatments, that required complete reconfiguration of the accelerator complex. During initial stages of Bevalac operation many of the experiments were of a survey nature, and could be run in shorter blocks accommodating the weekend and evening shifts available outside the therapy program. However, once the nuclear physics experiments became more sophisticated, weeks of continuous running were needed to gather required data. This increasingly-prevalent incompatibility led to substantial conflicts between the major research programs.

Valiant efforts were made, and significant accomplishments achieved, in increasing the flexibility of Bevalac operations, allowing rapid changes of configuration to accommodate as best as possible the needs of the different users, however the ultimate limitations of the very old accelerator technology inherent in the 1950's era Bevatron provided roadblocks to achieving the degree of flexibility required to make these efforts completely successful.

The end result was the need to compromise on many of the goals of each of the programs: the clinical program had to limit the number of patients treated; while the nuclear physics programs were limited to less than desired blocks of time for their larger experiments.

The clear lesson is that one should be very cautious about planning a clinical program on an accelerator dedicated to also conducting a first-line nuclear-physics program. Preferable is to have an accelerator dedicated to clinical treatments. If other programs wish to avail themselves of beams not required by the therapy program, this could be accommodated assuming that priorities are never lost sight of, and expectations of the parasitic programs never raised to conflict with the needs of therapy.

It should be noted, as well, that close proximity to hospital facilities, including extensive diagnostic capabilities and patient support facilities, should be very high on the priority list of designers of dedicated medical accelerator facilities. Bringing patients to a physics research complex is definitely less desirable than bringing the accelerator systems to the hospital complex.

<u>Current picture in US</u>

In spite of the good results from the Berkeley experience, and the strong proton programs at the Harvard Cyclotron Laboratory – Massachusetts General Hospital group in Boston, the US has been slow in building new hadrontherapy programs.

Two dedicated therapy facilities are currently operating, both with protons: the Loma Linda University Proton Therapy Facility, close to Los Angeles, California, and the new Northeast Proton Therapy Center at MGH in Boston. Both of these were built almost entirely with private funding. News has just arrived that MD Anderson Cancer Center has signed agreements to build a new proton therapy center in Houston, TX. This is the first of several proton initiatives to reach the stage of actual approval for construction. There is no current therapy capability with any ion heavier than protons, nor are there any immediate plans for developing this capability in the US.

Realistically, in the US today construction and operation of this type of facility are having to rely primarily on non-government sources of funding. Thus, economic arguments take precedence over clinical ones. Operating revenue must cover not only ongoing operating costs, but also amortization of outstanding construction loans. It is extremely difficult to develop a favorable model under these circumstances. A proton facility, with its somewhat lower capital costs, becomes somewhat more attractive than a substantially larger carbon-beam facility; but even so, in view of extreme pressure today on reducing costs within the US medical system, it is very difficult for a private hospital to justify embarking on this type of endeavor. Great credit is to be given to those institutions who have persevered!

The reasons for difficulty in obtaining government funding for construction or operation of such facilities is complex, and can best be traced to the compartmentalization of science-funding agencies. Large, expensive research facilities are typically built and operated by the Department of Energy for the broad scientific research community. However, DOE does not have a strong presence in the life-sciences area, this being the purview of the National Institutes of Health. NIH (of which the National Cancer Institute is a member) operates more on the mode of providing research grants for addressing specific scientific or medical questions, and is much less inclined to provide the expensive research facilities in which this research can be performed. New laboratories or facilities are expected to be provided by the (private) hosting hospital or institution. Thus, for instance, NCI funded the clinical research program at the Bevalac, but the Bevalac itself was a DOE facility primarily designated for use by the nuclear-physics community. DOE would argue today that it is not within its mission to build and operate an accelerator facility dedicated to clinical research and treatments. NCI, on the other hand, is placing today more emphasis on research on gene therapy and other more systemic therapies, and seems to place less priority on finding a solution to the problem of obtaining funding and support within other agencies for building hadrontherapy facilities for the US community.

International Outlook

Fortunately, the situation for hadrontherapy with carbon beams is not as bleak elsewhere in the world. After the closure of the Bevalac, initiatives were undertaken both in Japan and in Europe to continue the research with these beams. These efforts have definitely borne fruit. Japan has now two operating facilities with carbon beams: HIMAC[15] in Chiba and the Hyogo Hadron Therapy Center[16] at the Harima Science Garden City close to Kobe. GSI in Darmstadt, Germany has an active therapy program with carbon[17], and several new initiatives are making rapid progress: ETOILE in Lyon, CNAO in Milan, Med-AUSTRON in Wiener Neustadt. Construction is actually starting on HICAT, a new carbon-beam facility in Heidelberg.

Exciting results emerging from the programs at GSI and HIMAC, as reported in this conference[18] continue to build the case for light-ion therapy. Two specific examples: the precision treatments at GSI clearly show the viability for delivering high doses to complex fields in close proximity to critical structures, thus providing a viable treatment option for many patients. The hypofractionation studies for hepatocarcinoma at HIMAC, in which the full treatment is delivered in only 4 fractions, point to the possibility of significant increases in patient flow, and a substantial improvement in the economics of treatment delivery with these beams.

New research results will continue to build this case, and as the new carbon facilities are built and come on line, the rate of progress will be even higher. It seems inevitable that at some point in the future, the US will follow the path now being laid in Europe and Japan, and build its own carbon-therapy facilities. It is our fervent hope that this time will not be too far away!

Acknowledgments

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