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REVIEW

Proton therapy

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Abstract

Proton therapy has become a subject of considerable interest in the radiation oncology community and it is expected that there will be a substantial growth in proton treatment facilities during the next decade. I was asked to write a historical review of proton therapy based on my personal experiences, which have all occurred in the United States, so therefore I have a somewhat parochial point of view. Space requirements did not permit me to mention all of the existing proton therapy facilities or the names of all of those who have contributed to proton therapy.

Historical background

In 1946 Robert Wilson suggested that protons might have a role in cancer therapy due to their advantageous dose distributions (Wilson 1946). When proton beams interact with matter they produce energy depositions that are characterized by a relatively low dose in the shallow regions of their path; however, near the end of the proton range the dose rises sharply to a peak and then falls abruptly to zero (figure 1). Therefore, a high dose of ionizing radiation can be delivered to a deep-seated tumour while not exceeding the tolerance dose of the intervening normal tissues, and no dose will be given to normal tissues beyond the tumour. Wilson also proposed several innovative concepts that were subsequently used in the delivery of proton beams in cancer therapy including the use of range modulation wheels for producing spread-out Bragg peaks (SOBP) that cover larger targets than can be treated with pristine Bragg peaks (figure 2).

E O Lawrence developed the cyclotron at the University of California Lawrence Berkeley Laboratory (LBL) in 1930 and won the Nobel Prize for this work in 1939. As in photon therapy, the advances in proton therapy are closely tied to advances in accelerator technology. The first use of proton beams for the treatment of human patients was carried out by C A Tobias, J H Lawrence and others on the 184 inch cyclotron at LBL in the mid 1950s. They treated the pituitary gland with beams that passed entirely through the brain in a path that intersected the pituitary gland. They also used Bragg peak techniques that stopped the Bragg peak in the pituitary target (Tobias *et al* 1958). The LBL group began to use the

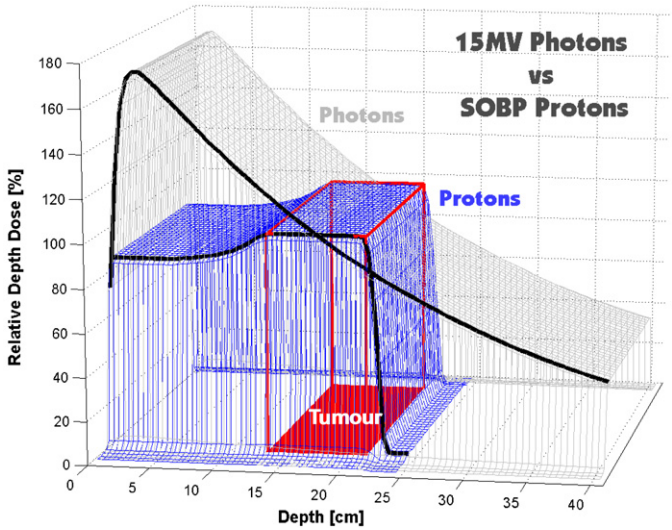

Figure 1. A comparison of depth doses for 15 MV photons and range/intensity modulated protons of variable energy. The proton spread-out Bragg peak (SOBP) has been developed so as to provide a region of high, uniform dose in at the tumour target shown in solid red. The red lines indicate an 'ideal' dose distribution that is uniform within the tumour region and zero elsewhere. The proton SOBP shows much better conformality to the tumour target than does the photon dose distribution. The advantage of protons is that the dose proximal to the tumour target is lower than that for photons and the dose distal to the tumour target falls rapidly to zero while the photon dose continues to decrease exponentially.

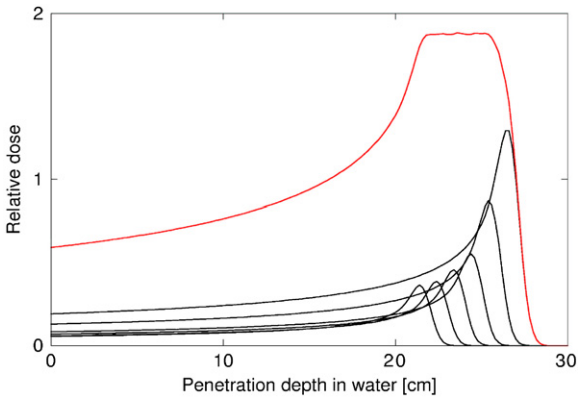

Figure 2. Range and intensity modulation of Bragg peaks to achieve a spread-out Bragg peak (SOBP). SOBPs can be produced by use of a physical device (ridge filter or modulation wheel) or by energy selection from the accelerator in conjunction with variable weighting of each individual Bragg peak. SOBPs can be produced for variable widths.

184 inch cyclotron to accelerate helium ions for cancer therapy in 1957 and treated patients on that accelerator until 1992.

In the late 1950s B Larsson and L Leksel, working at the Gustaf Werner Institute in Uppsala, Sweden, developed radiosurgical techniques for the treatment of brain tumours using proton beams from the Uppsala cyclotron (Larsson *et al* 1958). They were the first to

use range modulation to form a uniform region of dose along the beam path (an SOBP) and to use beam scanning to produce large treatment fields in the lateral dimension.

In 1961, Dr Ray Kjellberg, a neurosurgeon at the Massachusetts General Hospital (MGH), and colleagues began treating small intracranial targets with radiosurgical techniques at the Harvard Cyclotron Laboratory (HCL) in Cambridge, MA (Kjellberg *et al* 1962). These treatments evolved into a programme that continues today at the new MGH proton therapy facility, the Northeast Proton Therapy Center (NPTC). Andy Koehler, the HCL director, and his physics group worked with Kjellberg to develop the instrumentation, methodology and techniques for radiosurgical beam delivery. It is interesting to note that these treatments were carried out without the aid of modern imaging techniques; recent reanalysis of this work indicates that the original techniques worked quite well.

During the late 1960s and the decade of the 1970s, there was activity in proton therapy at several other physics research facilities around the world. Russia was particularly active with proton therapy programmes beginning at the Joint Institute for Nuclear Research in Dubna in 1968, the Moscow Institute for Theoretical and Experimental Physics in 1969, and St Petersburg in 1975. The National Institute for Radiological Sciences in Chiba, Japan started treatments in 1979 and it was there that a spot scanning system for proton treatment delivery was developed in 1980.

In the late 1980s and into the 1990s there was a flurry of activity in proton therapy around the world with significant programmes starting in Clatterbridge, England in 1989, France at Nice and Orsay (1991), iThemba Labs in Cape Town, Africa (1993), PSI at Villigen, Switzerland (1996), HMI in Berlin, Germany (1998), NCC in Kashiwa, Japan (1998), and Dubna, Russia (1999).

In 1975 a heavy ion therapy programme began at the LBL using the BEVELAC accelerator. Physicians and medical physicists from the University of California at San Francisco provided the medical expertise; high energy and accelerator physicists from LBL provided the beam delivery technology and software (Lyman *et al* 1979). Several advances in the technology of charged particle beam delivery that have had importance in proton therapy were developed at LBL. These developments included a 'beam wobbling' technique used to spread the heavy ion beams laterally. The LBL heavy ion programme was terminated in 1992.

The first hospital-based proton therapy facility in the United States was built at Loma Linda University Medical Center (LLUMC) in Loma Linda, California in the late 1980s; patient treatments began there in 1990 (Slater *et al* 1991). This facility was the result of the vision and work of Dr James Slater who was the Chairman of the Department of Radiation Medicine. The facility has a 250 MeV synchrotron and three isocentric gantries. The synchrotron was designed and built at Fermi National Laboratory. Interestingly, the corkscrew gantries installed at Loma Linda were designed by Andy Koehler at the HCL, yet another important contribution to proton therapy from the HCL physics group (Koehler 1987). Dan Miller, the medical physicist at LLUMC, developed a very efficient proton treatment planning programme that has enabled the LLUMC group to treat the largest number of patients (about 10 500) of any proton treatment facility. Two review papers published in the mid 1990s are excellent sources of information on proton therapy (Miller 1995) and instrumentation for proton and light ion beams (Chu *et al* 1993).

During the design of the Loma Linda accelerator at Fermi National Laboratory in Batavia, Illinois, the Proton Therapy Cooperative Group was formed (PTCOG). The name has been changed to Particle Therapy Cooperative Group. The purpose of PTCOG was to give advice to the Fermi Lab in the development of the requirements and specifications for an accelerator to be used in a hospital-based proton facility. I believe that PTCOG has had a strong influence in the development of charged particle therapy. PTCOG has grown into an organization of

several hundred physicists, clinicians, accelerator physicists and vendors that have met twice a year since its inception in the late 1980s. About 350 people attended the most recent PTCOG meeting in Munich, Germany where Europe's first hospital-based high energy proton therapy facility, the Rinecker Proton Therapy Center, was built. Physicians have played an ever-increasing role at recent PTCOG meetings; many meeting sessions are now devoted to the discussion of clinical protocols and results. Michael Goitein was the first chairperson of PTCOG, Gudrun Goitein, the Medical Director of the proton therapy programme at the Paul Scherer Institute (PSI) in Villigen, Switzerland was the second chairperson—I currently hold that position.

Neutrons—my first experience with particle therapy

In the same period that proton therapy programmes were beginning at physics research facilities in several countries, there was considerable interest in neutron therapy. In 1972 the University of Texas M D Anderson Cancer Center (MDACC), in collaboration with Texas A&M University at College Station, Texas, began the development of a neutron therapy programme. David Hussey, a physician at MDACC, led the clinical team and Peter Almond, with whom I was working at the time, led the initial physics efforts to start up the neutron therapy programme. Jim Smathers, a nuclear engineer at Texas A&M, was in charge of the group at the A&M cyclotron that developed the beam lines and instrumentation for patient treatments.

Physicians and physicists were excited about the gains that might be achieved with neutron therapy. They were particularly fascinated with the prospect that neutrons, with their high linear energy transfer (LET), would provide a tool for treating large tumours that were resistant to photons due to a lack of sufficient oxygen in their core regions. High LET particles had been shown to overcome the oxygen effect in studies using cell cultures and there was reason to expect that such gains would also be found in solid tumours. The concept that one could directly cause damage to the DNA by use of high LET radiations, rather than depend upon 'indirect' damage through the action of oxygen-dependent interactions, caused a lot of enthusiasm for neutron therapy programmes. During the 1970s and 1980s this enthusiasm led to the establishment of six neutron therapy programmes in the United States.

Neutron therapy led to a greater awareness of the need to incorporate biological effects into treatment planning. Neutrons have a relative biological effectiveness (RBE) of three (3) with respect to cobalt 60 and it was necessary to calculate dose distributions that included this biological effect. I worked with Ken Hogstrom at MGH to develop treatment planning methods for neutrons. Ken was later to contribute significantly to the treatment planning development for negative pi-mesons and electrons. Some lessons about neutron therapy were learned painfully. One of these lessons was that one cannot predict late effects from early effects for high LET radiations. Patients suffered much stronger late effects than would have been predicted from the observation of early effects such as skin and mucosal reactions. These early lessons proved to be valuable when carbon ions were first used for cancer therapy; carbon ions have about the same RBE as neutrons. Another finding was that neutron spectra from different target and accelerated particle interactions could lead to significantly different RBEs in neutron beams and one had to very carefully measure the RBE at each neutron facility. It is not clear whether or not the RBE for protons is influenced by proton scattering in double scattering systems of proton beam delivery nozzles—it is possible that proton RBE is slightly different for beam scanning and passive scattering systems. I expect that, since the RBE for protons is small (about 10% higher than photons), this effect would be hard to measure.

The first installation of cyclotrons in a hospital environment for the purpose of cancer therapy was done for neutron therapy at the Hammersmith Hospital in England and at the University of Washington in Seattle, Washington, US. These projects were precursors to hospital-based proton therapy facilities. In the United States there were two neutron facilities built within hospital walls, one at the University of Washington and one at M D Anderson Cancer Center. Another important technology that was developed at this time was the isocentric gantry that was installed for the neutron therapy programme at the University of Washington. This gantry enabled physicians to break away from the restrictions of horizontal and vertical beam lines and deliver treatments using techniques very similar to those used for photon therapy. The nozzle on this gantry also contained a multi-leaf collimator that provided greater flexibility in shaping neutron fields and eliminated the need for radiation therapists to handle radioactive treatment collimators. All of these technologies paved the way for modern hospital-based proton therapy systems.

Negative pi-mesons—my first experience with charged particle therapy

In the early 1970s the University of New Mexico (UNM) Cancer Center in Albuquerque, New Mexico and the Los Alamos Meson Physics Facility (LAMPF), in Los Alamos began a collaboration to develop a research programme using negative pi-mesons to treat cancer. The leaders of this programme were Dr Morton Kligerman, the UNM cancer center director and Dr Louis Rosen, director of LAMPF. I joined the pion team in 1974.

I think the combination of three charged particle therapy projects contributed many concepts, technologies, tools and clinical data that have been important in the development of proton therapy. These three projects operated concurrently for many years with significant collaboration among the projects, especially among the medical physicists. These projects were: The MGH/HCL proton therapy programme in Boston/Cambridge, Massachusetts; the LBL/UCSF heavy ion therapy programme at the Lawrence Berkeley Laboratory, Berkeley, California; and the UNM/LAMPF negative pi-meson (pion) therapy programme at the Los Alamos National Laboratory in New Mexico. The MGH/HCL project made especially important contributions to proton therapy and advanced the technology and clinical knowledge to a significant degree. I think it is also true that many of the developments in charged particle therapy have had important consequences for photon therapy; however the technology transfer from particles to photons has not been well documented or widely recognized.

Three-dimensional treatment planning and range compensation

Charged particle beams stop in tissue at depths determined by their incident energy and interactions in tissues traversed in their path. Therefore, in order to shape the stopping beam to the distal surface of the target volume, one must know the details of the anatomy in the treatment volume including the location and density of each tissue element. In the 1970s, photon therapy was essentially conducted in a two-dimensional framework with regions of interest (target and critical normal tissues) determined from planar radiographs; CT scanners were only starting to be introduced and used for radiation therapy. It was imperative that three-dimensional knowledge of the tumour and normal anatomy be obtained in order to treat patients with charged particles.

The three charged particle programmes, MGH/HCL, UCSF/LBL and UNM/LAMPF, were, to my knowledge, the first radiation therapy programmes to install dedicated CT scanners. Since the therapy beams at both HCL and LBL were horizontal, patients were treated in a sitting position; these facilities purchased and modified CT scanners for vertical scanning

capabilities so that patients could be scanned in the sitting position. The pion transport channel in Los Alamos was vertical, therefore we were able to use a conventional CT scanner and scan patients in supine or prone positions. There was a period before the CT scanner was installed in Los Alamos that we had to send patients to either California or Colorado to obtain CT scans because a CT scanner was not available in New Mexico.

Each of the three charged particle programmes entered into an intense programme to develop volumetric treatment planning capabilities. At MGH, Michael Goitein developed a proton treatment planning system. Goitein's system evolved over the years and he published this work in a series of articles during 1983 (Goitein *et al* 1983a, 1983b, 1983c). Goitein's treatment planning system has been the best known and most utilized of the proton treatment planning systems and variations of this system are still in use at some proton facilities. He incorporated several important treatment planning tools into his system including 'beams eye view', 'dose volume histograms' and 'error analysis'—these tools have been utilized in virtually every modern treatment planning system. There is no doubt that Goitein's work in this area was seminal and his treatment planning system served as a model for the development of three-dimensional photon treatment planning. In the mid 1990s this system was upgraded to use a pencil beam dose calculation algorithm—Linda Hong, a post doctoral fellow at MGH was responsible for developing this model (Hong *et al* 1996).

Another three-dimensional system that is essential for passive scattered charged particle therapy is range compensation. Range compensation allows shaping of the dose to match the distal surface of the target volume. It corrects for the shape of the patient surface, the tissue inhomogeneities (air, bone, etc) in the beam path and the shape of the distal target volume surface. A range compensator was used in Los Alamos for every patient treatment field. In the beginning, the compensators were calculated by hand and a three-dimensional model was constructed by use of Styrofoam. This model was then used to construct a mold that was then poured with wax to form a three-dimensional range compensator. At Los Alamos, the downstream side of the compensator was formed to fit the patient surface in order to allow the compensator to fit snugly and minimize the air gap, thus lateral penumbra, of the treatment beam. We also developed techniques to shape the dose to the proximal surface of the target volume in those cases where there were critical structures proximal to the tumour. To my knowledge, this was the first use of both the 'double-sided' range compensator and shaping to the proximal target volume surface. At both HCL and LBL range compensators were made on milling machines using acrylics such as Lucite. At MGH, Goitein developed a method for incorporating patient set up and calculation errors into the range compensator in order to compensate for small misalignments between the compensator and target volume.

Image-guided radiation therapy

The use of imaging to guide the beam delivery process is currently a topic of great interest in radiation therapy. This practice, in fact, goes back to the early charged particle days when imaging techniques were used to align the patient for each treatment field. Because of the precision required for high dose particle therapy, the desired alignment of the target to the beam could only be achieved with imaging techniques. In Los Alamos, an imaging suite was set up outside the treatment room to assure the correct patient set up. The patients were then aligned with lasers and transported to the treatment room on a couch that efficiently and accurately docked with a ram that rose out of the treatment room floor. The treatment aperture and range compensator were fixed to the couch and also aligned with lasers outside the treatment room. In this manner, patients could be exchanged quickly while maintaining an accurate set up position. The dose rates on the pion beam were very low and this transfer mechanism was

necessary in order to reduce the time in the treatment room required to treat patients. At both HCL and LBL imaging systems were installed in the treatment room that allowed stereotactic imaging to be performed in order to accurately position the patient for each treatment field. The imaging systems developed at the early charged particle facilities were precursors to the on-board-imaging systems that are currently being implemented in modern radiation therapy facilities.

Intensity modulation

Intensity modulation techniques were used in charged particle treatments in the 1970s although admittedly in somewhat simple forms. The pristine Bragg peaks of charged particle beams are too narrow to treat any but the smallest of targets such as the pituitary gland. In order to spread out the dose distribution in depth, range modulation was developed. This took the form of both spinning propellers and ridge filters that placed multiple layers of absorbers in the beam for various time periods in order to control the weight of each individual Bragg peak in order to achieve a uniform spread-out Bragg peak tailored to match the greatest extent of the target volume in depth (figure 2). This method of achieving SOBPs is simple intensity modulation. Another aspect of intensity modulation, the use of several non-uniform fields to achieve an overall uniform dose distribution in a target volume, was also used in a primitive form to treat concave target volumes associated with tumours such as skull base chordomas and chondrosarcomas. Modern day proton therapy utilizes scanning spot beams to achieve full-blown intensity modulation.

During this early period of charged particle therapy we collectively addressed other problems that impacted future particle therapy and, in particular, proton therapy. During attempts to develop a satisfactory framework to quantify the absorbed dose for clinical pion beams it became clear that the charged particle community was in need of absorbed dose comparisons and common protocols for the measurement and calculation of heavy charged particle absorbed doses. I applied to the National Cancer Institute and received funds to form a cooperative group among the charged particle physicists that would hold workshops, undertake dose comparisons using charged particle clinical beams and develop a protocol for the calculation of absorbed dose for charged particle beams.

We began a series of workshops to discuss the problems related to the measurement and statement of absorbed doses and held a number of comparisons during which we met at one of the facilities and, using our respective ionization chambers, electrometers, and methodologies, took measurements in the respective beams (protons, pions or heavy ions) and compared the results. At that time we had agreed to use tissue equivalent gas in our ion chambers with the idea that such gas would more nearly match the tissue equivalent plastic walls of the chambers and thereby decrease the magnitude of the correction factors, which in turn would decrease the errors in the final statement of absorbed dose. This choice, however, created the need to standardize the composition of tissue equivalent gas and to control the gas pressure (flow rate) in the ion chambers.

The Bragg–Gray cavity theory was the logical basis for the development of the framework for absorbed dose measurements. The primary problems related to our use of this formalism were associated with the choice of the W-values and stopping power ratios for the various particles. We decided to use calorimetry to determine the product of the W-value and the ratio of stopping powers (chamber gas to chamber wall) that occurs in the Bragg–Gray equation. Calorimetry was the gold standard for absorbed dose measurements at that time and Steve Domen at the US National Bureau of Standards was considered to be the guru of calorimetry. A calorimeter had also been developed at Yale University by a group headed by Robert

Schultz. I invited Steve Domen to visit Los Alamos to measure the absorbed dose for the pion beams; the group from Yale visited HCL and worked with Lynn Verhey to perform calorimetry measurements there (Schultz *et al* 1992).

During the course of these measurements the Charged Particle Dosimetry Working Group met regularly to write the dosimetry protocol. The Charged Particle Dosimetry Protocol was published as AAPM Report (No. 16) in 1986 with John Lyman at LBL spearheading the final effort. In 1991 a working group of the European Clinical Heavy Particle Dosimetry Group (ECHED) issued a protocol entirely dedicated to proton beams that advocated the use of air in the cavity chamber and this practice eventually replaced the use of tissue equivalent gas (Vynckier *et al* 1991).

The end of the pion therapy programme at LAMPF came in 1981 when the NCI decided to stop funding the clinical research. The LAMPF programme proved the feasibility of using pions to treat cancer and, based on the Los Alamos experience, pion clinical programmes were started at the TRIUMF accelerator in Vancouver, Canada and at the SIN accelerator (now called the Paul Scherer Institute (PSI)) at Villigen, Switzerland. Both of these pion programmes continued for several years but were later converted to proton therapy.

On the last day I was in Los Alamos one of the Los Alamos physicists asked what I thought the future would hold for charged particle therapy. I replied that proton therapy was the most likely to survive and play an important role in radiation therapy. Asked why, I responded that protons provided excellent dose distributions, almost as good as those of helium and heavier ions, and proton accelerators could be developed that had small enough size and low enough cost for hospital-based operations.

The National Cancer Institute

I spent three years at the National Cancer Institute where my responsibilities included work involving charged particle therapy. I established programmes for the evaluation of treatment planning for external beam photons, electrons, heavy particles and radio-labelled antibodies. A working group composed of physicians and physicists from several institutions was formed for each programme.

While I was at Los Alamos, I had been asked to conduct a comparison of particle treatment planning and present the results at an RSNA meeting in Chicago. The aim was to compare dose distributions from protons, pions and heavy ions in order to evaluate their relative advantages. Targets and critical structures were identified on CT scans that were sent to medical physicists at MGH for proton planning and to LBL for heavy ion planning. Treatment plans for pions were calculated at Los Alamos. The main conclusion of this study was that the state of the treatment planning systems at that time did not allow one to conduct a meaningful treatment planning comparison among the various particles.

It was with this experience in mind that I wrote the requirements for the programmes for Photon and Particle Treatment Planning Evaluation. A central requirement was that each of the participants must provide three-dimensional treatment planning systems or develop such capability during the initial phase of the projects.

The participants of the evaluation studies put tremendous efforts into developing three-dimensional treatment planning systems and, at the conclusion of the projects, each institution had evolved and developed their systems to the extent that respectable three-dimensional treatment plans could be calculated, displayed and analysed. It has been said that these cooperative working groups provided a much-needed impetus for the rapid development of three-dimensional treatment planning for both photons and charged particles (Smith and Purdy 1991).

Proton therapy

In about 1972, Herman Suit became Chief of the Department of Radiation Medicine at the MGH. Dr Suit recognized that the proton beams at HCL, where radiosurgery was being carried out, also provided the potential to improve outcomes in large-field, fractionated cancer treatments (Suit *et al* 1975). He recruited Michael Goitein to assist him in starting such a programme at the HCL. They applied to the National Cancer Institute for funds to conduct cancer treatment research using proton beams; the grant application was approved and they started treating patients on the HCL proton beams in 1974. This NCI grant has been continuously funded through renewal applications and is currently funding proton therapy research at the MGH Northeast Proton Treatment Center. Koehler and his group at HCL collaborated with Herman Suit and his colleagues to provide beam delivery technology, instrumentation and dosimetry for this new programme. Koehler developed the use of passive scattering to spread proton beams for the treatment of large tumours and also developed range modulation wheels to produce SOBPs to cover extended target volumes (Koehler *et al* 1975, 1977).

I went to MGH in 1992 to participate in the development of a hospital-based proton therapy centre and to lead the clinical physics group working at HCL. The MGH/HCL programme had produced impressive clinical results in several disease sites. One of the most successful treatments was for ocular melanoma—Drs Evangelos Gragoudas at the Massachusetts Eye and Ear Infirmary and John Munzenrider at MGH were leaders in this effort. Michael Goitein developed many of the treatment techniques and the treatment planning system for ocular melanoma treatments. Other impressive clinical results were obtained for chordomas and chondrosarcomas of the skull base and cervical spine and for nasopharynx and paranasal sinus tumours. Drs Norbert Liebsch, Eugen Hug, Allan Thornton and others contributed significantly to this work. Drs William Shipley and Anthony Zietman conducted a clinical trial for prostate cancer in collaboration with physicians at Loma Linda Medical Center.

However, HCL was an ageing facility built for basic physics research; it was remote from MGH; and its capacity was saturated. Studies were conducted on the feasibility of expanding and upgrading HCL; however it was decided that this would be too expensive. In addition, Harvard University had long-term plans to develop the HCL site for other uses.

In the early 1990s the decision had been made to construct a hospital-based proton therapy facility at MGH. Herman Suit and Michael Goitein decided that the clinical results obtained at HCL, along with the fact that the HCL capacity was saturated, justified the building of this new facility. The challenges of this venture were to obtain funding for the facility, find a site for it on property at the MGH main campus, which was largely already developed, design and build the facility and equipment, and transfer the proton clinical programme from the HCL to the MGH. As is usual for such large undertakings, it took longer than expected to accomplish all of those tasks.

Jay Flanz, an accelerator physicist at the MIT Bates Accelerator, was recruited to help with the development of the new facility. Our first task was to write grant applications to the NCI for funding of the preliminary work and, afterwards, for funding of the construction of the building and equipment. The NCI decided that they would only fund one-half of the construction costs for the facility and MGH had to fund the other half. MGH agreed to do this and the project was officially started.

The treatment programme at the HCL continued without pause during the development of the new facility. One of my first goals for HCL was to increase the number of patients under treatment. In 1992, 12 to 13 patients per day were being treated and I was concerned that too few patients were being entered into the NCI-funded clinical protocols. The throughput

of treatment planning was considered at that time to be a limiting factor; there were also inefficiencies in the procedures and systems of setting up and treating patients. Within 2 years we were treating about twice the number of patients—this greatly enhanced our position with respect to the NCI grant because it led to greater numbers of patients being placed on treatment protocols.

Another goal was to implement ionization chamber methodology for measuring proton absorbed dose as described in the AAPM and ECHED protocols. From the beginning of the HCL clinical programme Faraday cup methods had been used to determine the absorbed dose for therapy beams and, while this method should produce equivalent results with ionization chambers, we found that the ionization chamber results differed from the Faraday cup measurements by about 6%. This was probably due to low energy protons in the beam that caused the mass stopping power to be different than expected. Also the beam was probably more elliptical in shape than it was originally thought to be and, if so, the beam area used in the Faraday cup calculations was not correct. The 6% difference in dosimetry was confirmed by comparisons with several other proton groups during comparative measurements at Loma Linda. A dose comparison conducted in a 1995, during the time that Faraday cup measurements were being used the MGH/HCL, showed that Faraday cup measurements were about 5 to 6% lower than the average for the other participants (Vatnitsky *et al* 1996). The Faraday cup calibration was transferred to the ionization chamber that was used in the Loma Linda measurements. In a similar dose comparison conducted in 1998, held after the dosimetry at HCL had been changed to a protocol based on ion chambers, the dosimetry agreed with the average of the results of all participants within 1% (Vatnitsky *et al* 1999). After finding the 6% discrepancy in dosimetry at HCL, and confirming this finding through comparisons with other facilities, we changed the statement of absorbed dose and the HCL treatments were adjusted to give patients the same dose before and after the dosimetry change so that clinical outcomes would remain constant.

Meanwhile, the development of the new facility at MGH was launched. Ion Beam Applications (IBA), a Belgium firm, was awarded the contract for the proton therapy equipment and the treatment control and safety systems. Patient treatments were expected to begin at the NPTC in 1998. The NPTC was to have a cyclotron accelerator, two isocentric gantries and a fixed beam room with horizontal beams for ocular melanoma treatments and for radiosurgery. There were several novel aspects of the NPTC beam delivery system—the nozzles had the ability to use both passive scattering and beam wobbling techniques to spread the beam laterally and the range modulation wheels were contained completely within the nozzles. The beam intensity incident upon the modulation wheels was modulated in such a way as to extend the energy range over which the wheels could achieve uniform spread out Bragg peaks (Flanz *et al* 1997).

Unfortunately, there were problems in the development of the control system that led to a delay in the project. Treatments began at the Northeast Proton Therapy Center in October 2001. Treatments were stopped at the HCL in mid 2002 and that facility was torn down. A great amount of the history of proton therapy happened at the HCL and the physicists there, as well as the MGH clinical group, made some important advances in both the technical and clinical aspects of proton therapy.

There was another MGH effort that was pivotal for the future of proton therapy. As the planned opening date for the NPTC approached, we became concerned about reimbursement of proton therapy. At that time there were no approved procedures for proton therapy and proton treatments were being reimbursed by use of a special procedure code. We believed that proton therapy had advanced to the point that we should seek proton therapy treatment procedure codes and then negotiate with the federal government and insurance carriers to

assign reimbursement rates to those codes. We wrote an application to the American Medical Association for proton treatment delivery procedure codes and were awarded codes for simple and intermediate treatment delivery. At a later date we worked with Lima Linda to achieve a complex treatment delivery procedure code. We were successful in working with Medicare, the federal health care programme, and regional insurance carriers, to obtain reimbursement rates for the new procedure codes. As a result of these efforts, when the NPTC opened, the MGH was able to charge for and be reimbursed for proton treatment delivery in the same manner as for photon treatments. Importantly, when Medicare approved the reimbursement rates, they said that proton therapy was no longer investigational—proton therapy had been accepted as a standard treatment for many disease sites.

In the early 2000s, proton therapy had reached the point where it was considered to be financially viable and technically feasible for routinely application within the confines of a hospital environment. I think this came about for the following reasons:

- Clinical results achieved by use of proton beams were impressive. Each disease site that had been treated had been shown to have increased local control compared to photons and, in most cases, reduced late effects (Spiro *et al* 2001).
- Proton treatments were being reimbursed by both private insurance carriers and government health agencies. Also, private investors were more likely to provide funding for proton therapy facilities because there was a reasonable assurance for a return on their investments.
- The Loma Linda proton therapy facility was the first hospital based proton facility and it paved the way for others to follow. The NPTC provided additional evidence of the feasibility of hospital-based proton facilities and MGH's status as an internationally acclaimed academic hospital, associated with Harvard Medical School, provided additional measures of credibility for hospital-based proton therapy.
- Several vendors begin to offer hospital-based proton therapy systems because a viable market for suppliers of proton therapy equipment had been created. This also brought competition and technical innovation to the proton therapy market place.

After the NPTC project I was fortunate to be able to participate in the design and building of a proton therapy facility at one of the leading cancer hospitals in the world, the University of Texas M D Anderson Cancer Center (MDACC), located in Houston, Texas, US. This was particularly interesting for me because M D Anderson was the place where I started my Medical Physics career in 1970. The M D Anderson Proton Therapy Center will have a synchrotron accelerator, three isocentric gantries and one treatment room with two horizontal beam lines, one for treating large fields and one for treating ocular melanoma. Two of the gantries will have highly efficient passive scattering nozzles and one gantry will have a spot-scanning nozzle for intensity modulated proton treatments (IMPT); this nozzle may deliver the first IMPT treatments in the United States. IMPT will allow dose distributions to be shaped in three dimensions and thus have higher dose conformality to the target volume than passive scattering treatment delivery systems. Another important advantage of IMPT treatments is the decreased production of neutrons due to the decrease of scattering materials in the treatment delivery nozzle and because spot beams, if sufficiently small, can be delivered without beam-shaping apertures that contribute to neutron production. Hitachi Ltd, a Japanese firm furnished the equipment for the Houston facility. The MDACC proton therapy facility will open in mid 2006. It is designed to be a high capacity facility that will treat patients two shifts per day, 6 days a week. To my knowledge, the MDACC proton facility is the first fully integrated facility in the sense that all imaging, treatment planning, machine shop, treatment billing, electronic charting and treatment delivery systems are networked utilizing a data management system

developed by IMPAC. Varian Medical Systems provided the treatment planning systems. If proton therapy is to become successful as a hospital-based modality, it must have equivalent infrastructure, networking and integration to that of modern photon therapy.

I have mentioned the PSI in Switzerland in regard to their pion therapy programme that lasted from 1980 until 1993. In 1984 they started a proton therapy programme with 72 MeV proton beams and have treated 4182 patients with eye tumours. In 1996 they began treating patients with a 200 MeV beam using spot scanning techniques and have recently treated patients using IMPT techniques—the first IMPT treatments to be delivered with protons. PSI is now constructing a new proton therapy capacity at PSI using a cryogenic cyclotron and will deliver IMPT treatments using small spot beams. This facility will open in late 2006.

Another US proton facility will open in Jacksonville, Florida in 2006. The Rinecker Proton Therapy Center in Munich, Germany will also open in 2006; this facility will have only spot beam scanning capability—the Rinecker Center is the first large-scale proton therapy centre to rely completely on beam scanning for treatment delivery. Of particular note, a carbon ion and proton facility is being built in Heidelberg, Germany, the first hospital-based facility that will have both carbon ion and proton beams. At the present time, about 25 facilities around the world are treating patients with proton beams and over 43 000 patients have been treated. An additional ten facilities are either under construction or will begin construction very soon and more than twelve institutions are being planned.

The promises and challenges for proton therapy

The future for proton therapy is very promising. The improved dose distributions of proton beams, as compared with photons, will allow increased dose to be delivered to target volumes, which will translate into improved local control and disease-free survival. Also, the reduced dose to non-involved organs and tissues will translate into reduced morbidity and improved quality of life, especially for paediatric patients. This will also allow increased intensity and improved treatment compliance for chemotherapy when used concurrently with radiation therapy.

I think the challenges for proton therapy include the following:

- To use proton beams optimally. Used inappropriately, or without proper optimization, proton dose distributions may be no better, or even worse, than those for photon intensity modulated treatments.
- To reduce the cost of proton therapy.
  - Current facilities are one-of-a-kind and prototype technology is very expensive. Multiple installations of a particular design will reduce capital equipment costs because the cost per unit will be decreased (economy of scale).
  - Most of the costs of proton therapy (capital and personnel) are fixed, therefore proton therapy must be made more efficient so that more patients can be treated and the fixed costs can be spread among a greater number of patients.
- To optimize the efficiency of IMPT. IMPT will result in improved dose distributions and fewer neutrons will be produced than when passive scattering techniques are used. However it may be difficult to deliver IMPT treatments in the same time as required for passive scattering and, if so, fewer patients can be treated.
- To quantify proton RBEs for specific tumours and normal tissues. This will permit the optimization of biological dose and therefore improve treatment outcomes.
- To conduct clinical investigations in those disease sites that have not yet been shown to be better treated using proton beams.

- To train physicians, physicists, therapists and dosimetrists in proton therapy. There is a substantial shortage of personnel that are experienced in proton therapy.
- To build more proton therapy facilities. For many disease sites there is no justification for using photons if proton beams are available—this is especially true for paediatric patients. Proton therapy is often not available to patients who can benefit from this important treatment modality.
- To conduct clinical trials that compare protons and carbon ions. It has not been definitively shown that carbon ions result in improved clinical outcomes over those that can be achieved using proton beams. The physical dose distributions of carbon ions and protons are qualitatively very similar. Carbon ions may offer a biological advantage over proton ions; however they will be more expensive. Before building many carbon ion facilities we must determine that they will improve clinical outcomes. We do, however, need to build a few carbon ion facilities in order to conduct the necessary clinical research.

There is currently an increasing interest in building facilities that have both carbon ions and protons—one such facility is now operating in Japan and one is being built in Germany. Carbon ions will not be needed to treat all patients; however the primary treatment could be given with protons and a boost given with carbon ions.

It is almost certain that future proton therapy facilities will increasingly use scanned proton beams to provide IMPT treatments. We will also see new technologies such as laser accelerated proton beams and small cryogenic cyclotrons, both installed on gantries. There is also a pressing need to build smaller, less expensive proton facilities that can be placed in small hospitals. Finally, there may be a role for proton facilities that are dedicated to the treatment of specific tumours such as paediatric tumours (at large children's hospitals), eye tumours (at large eye clinics and hospitals) and for treating frequently-occurring cancers such as prostate and lung cancers.

It has been a privilege to be a participant in the development of proton therapy—I hope to be able to continue this work for some time. We are on the threshold of many advances in proton therapy technology and there are many challenges in implementing these new technologies so that they are safe, accurate and efficient.

References

American Association of Physicists in Medicine (AAPM) 1986 Protocol for heavy charged-particle therapy beam dosimetry *AAPM Rep. No. 16*

Chu W T, Ludgwigt B A and Renner T R 1993 Instrumentation for treatment of cancer using proton and light ion beams *Rev. Sci. Instrum.* **64** 2055–122

Flanz J, Durlacher S, Goitein M, Smith A and Woods S 1997 The Northeast Proton Therapy Center at Massachusetts General Hospital *Proceedings of Symposium of North-eastern Accelerator Personnel* (Woods Hole, MA: World Scientific) pp 51–8

Goitein M and Abrams M 1983a Multi-dimensional treatment planning: I. Delineation of anatomy *Int. J. Radiat. Oncol. Biol. Phys.* **9** 777–87

Goitein M, Abrams M, Rowell D, Pollari H and Wiles J 1983b Multi-dimensional treatment planning: II. Beams eye-view, back projection, and projection through CT sections *Int. J. Radiat. Oncol. Biol. Phys.* **9** 789–97

Goitein M and Miller T 1983c Planning proton therapy of the eye *Med. Phys.* **10** 275

Hong L, Goitein M, Bucciolini M and Comiskey R 1996 A pencil beam algorithm for proton dose calculations *Phys. Med. Biol.* **41** 1305–30

Kjellberg R N, Sweet W H, Preston W M and Koehler A M 1962 The Bragg peak of a proton beam in intracranial therapy of tumors *Trans. Am. Neurol. Assoc.* **87** 216

Koehler A M, Schneider R J and Sisterson J M 1975 Range modulators for protons and heavy ions *Nucl. Instrum. Methods* **131** 437–40

Koehler A M, Schneider R J and Sisterson J M 1977 Flattening of proton dose distributions for large-field radiotherapy *Med. Phys.* **4** 297–301

Koehler A M 1987 Preliminary design study for a corkscrew gantry *Proceedings of the Fifth PTCOG Meeting: International Workshop in Biomedical Accelerators (Lawrence Berkeley Laboratory, Berkeley, CA)* pp 147–58
Larsson B, Leksell L, Rexed B, Sourander P, Mair W and Anderson B 1958 The high-energy proton beam as a neurosurgical tool *Nature* **182** 1222
Lyman J T, Chen G, Kanstein L and Howard J 1979 Heavy particle facilities at the Lawrence Berkeley Laboratory *First International Seminar on the Use of Proton Beams in Radiation Therapy (Moscow, Atomistadt)* pp 122–35
Miller 1995 A review of proton beam radiation therapy *Med. Phys.* **22** 1943–54
Schultz R J, Verhey L J, Huq M S and Venkatarmanan 1992 Water calorimeter dosimetry for 160 MeV protons *Phys. Med. Biol.* **37** 947–53
Slater J M, Archambeau J O, Miller D W, Notarus M I, Preston W and Slater J D 1991 The proton treatment center at Loma Linda University Medical Center *Int. J. Radiat. Oncol Biol. Phys.* **22** 383
Smith A R and Purdy J A (eds) 1991 Three-dimensional photon treatment planning: Report of the Collaborative Working Group on the Evaluation of Treatment Planning for External Photon Beam Radiotherapy *Int. J. Radiat. Oncol. Biol. Phys.* **21** 1–266
Spiro I J, Lomax A, Smith A and Loeffler J S 2001 *Proton Radiation Therapy in Cancer: Principles and Practice of Oncology* 6th edn, ed DeVita, Hellman and Rosenberg (Philadelphia, PA: Lippincott, Williams and Wilkins) pp 3229–35
Suit H D, Goitein M, Tepper J, Koehler A M, Schmidt R A and Schneider R J 1975 Exploratory study of proton radiation therapy using large field techniques and fractionated dose schedules *Cancer* **35** 1646–57
Tobias C A, Lawrence J H, Born J L, McCombs R K, Roberts J E, Anger H O, Low-Beer B V A and Huggins C B 1958 Pituitary irradiation with high-energy proton beams: a preliminary report *Cancer Res.* **18** 121
Vatnitsky S *et al* 1996 Proton dosimetry intercomparison *Radiother. Oncol.* **41** 169–77
Vatnitsky S *et al* 1999 Proton dosimetry intercomparison based on the ICRU 59 protocol *Radiother. Oncol.* **51** 273–9
Vynckier S, Bonnett D E and Jones D T L 1991 Code of practice for clinical proton dosimetry *Radiother. Oncol.* **20** 53
Wilson R R 1946 Radiological use of fast protons *Radiology* **47** 487

Biography

Alfred R Smith has been involved in heavy particle therapy since the early 1970s and has worked with fast neutrons, negative pi mesons and protons. He has been involved in the development of treatment facilities as well as physics and patient treatment programs for these particles. From 1992 to 2002 he participated in the development of the Northeast Proton Therapy Center at Massachusetts General Hospital. In mid 1992 he moved to the M D Anderson Cancer Center in Houston, Texas to help develop a proton therapy facility that will provide standard proton treatments as well intensity modulated techniques using scanned beams.