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REVIEW OF ION BEAM THERAPY: PRESENT AND FUTURE

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Abstract

First therapy efforts at the Bevalac using neon ions took place in the '70's and '80's. Promising results led to construction of HIMAC in Chiba Japan, and more recently to therapy trials at GSI. Both these facilities are now treating patients with carbon beams. Advances in both accelerator technology and beam delivery have taken place at these two centers. Plans are well along for new facilities in Europe and Japan.

1 INTRODUCTION

Bragg peak therapy offers the promise of excellent dose localization for treatment of tumors. Research with proton and ion beams has been ongoing for almost 50 years, and many tens of thousands of patients have been treated [1]. Proton facilities are becoming more numerous now, with several located in hospital settings. Ion beam facilities have until now been slower in developing, mainly because of the size and cost involved.

Ions offer several advantages over protons. Being heavier, trajectories are stiffer so less multiple scattering and range straggling occur as beams penetrate to final treatment locations deep inside the body. This means that sharper field edges can be achieved, an important consideration for tumors close to critical structures. In addition, ionization density varies as Z^2, so, for instance each carbon ion deposits energy along its track equivalent to 36 protons. Thus localized biological damage is much higher, with greater cell-killing and less chance of repair.

Selection of the "ideal" ion to use for therapy involves minimizing radiation damage in normal tissue upstream of the target while at the same time maximizing cell-killing at the stopping point. Extensive radiobiological studies in the '70's at Berkeley pointed to neon as most promising; however long-term followup of the many patients treated at the Bevalac indicates larger-than-anticipated late-effects in the normal tissue [2]. As a consequence, trials at HIMAC and GSI are focusing on carbon ions. Note that other ions (even protons) may be best for certain treatments, depending on tumor type and location, and patient conditions. So, the ultimate treatment facility should offer a range of ions and treatment options.

1.1 System specifications [3]

Energy: To reach 30 cm in tissue, protons must have 250 MeV, carbon 425 MeV/amu. Maximum accelerator rigidity should not be less than 7 T-m. Performance must be good over the full energy range, as Bρ for maximum depth protons is 2.5 T-m, and lower energies (≈100 MeV – 1.5 T-m) will be desired as well.

Intensity: To treat a 20 x 20 x 10 cm volume in under 1 minute to 2 Gy requires ≈1 x 10^{10} protons per second, or ≈ 3 x 10^8 carbon ions per second delivered to the treatment field. As overall efficiencies in beam utilization can be as low as 10%, accelerator capability should be about 10 times higher. The inefficiencies arises either from absorption and collimation in passive scattering systems; from reductions in intensity to minimize effect of spikes in a noisy spill, or from various gating scenarios to compensate for patient motion.

Reliability: An accelerator system operating in a clinical environment must demonstrate reliability above 95%; facilities are being designed to treat over 200 patients per day, so beam must be available on demand at all times! 16-hour treatment days, 6 days per week are needed for 50 weeks per year, in addition to beam time for calibrations andQA checks.

Safety: Safety considerations are extremely important as well. Redundancy of dosimetry and control systems, and an extremely well-trained and constantly alert staff are mandatory. The technical performance and psychological intensity levels are greater than experienced at most accelerator facilities, and require particular attention in facility designs.

1.2 Dose delivery

Response of tissue to radiation is highly non-linear, rising steeply above a given threshold. This requires very accurate dose control in both treatment volume and normal tissue. Specified accuracy is ±2%, placing great demands on beam delivery systems. Treatment planning converts the dose desired in each target volume element ("voxel") to the number of particles to be delivered there; it is up to the beam delivery system to carry this out [4].

2-D delivery: The simplest "passive" delivery systems involve passing the beam through a compound scattering system which modifies the basic gaussian scattering distribution yielding a flat treatment field; good proton field sizes up to 30 cm diameter can be obtained by this technique.

For heavier, more rigid beams, scattering is less effective, and magnetic "wobbling" systems are used. These paint either concentric circles or a rectangular field, depending on magnet drive functions. Beam spot swept is fairly large (few cm FWHM); a reasonably uniform spill is required to ensure uniformity of field distribution.

In both cases, depth modulation of the field is obtained by using "ridge filters", such as brass plates with carefully-shaped grooves that present different thicknesses of slowing material to the beam. The resulting SOBP ("Spread-Out Bragg Peak") is tailored to produce the desired "iso-dose" distribution at each depth of the field. Families of such filters are used to obtain fields with different SOBP thicknesses.

Such delivery systems produce treatment fields with cylindrical symmetry; constant depth modulation over the whole field. The treatment volume is shaped by collimation to contain just the target, but normal tissue is included which receives the full therapeutic dose.

3-D delivery: Two types of "active" delivery systems can minimize normal tissue involvement, by forming the treatment field into an arbitrary 3-dimensional shape.

The first is uses "range-stacking" and an MLC (multi-leaf collimator). The collimator, with two sets of stacked bars typically 5 to 10 mm wide can be adjusted via actuators to any arbitrary shape. Beam is brought in at the maximum depth, the collimator is shaped to the desired treatment field at that depth. After delivering the dose at this depth the range of the beam is shortened, the field size is changed, and the next layer is treated; and so forth until the whole volume receives the prescribed dose.

The second is called "pencil-beam" or "raster" scanning. A small (5 to 10 mm) diameter beam is controlled in the transverse direction by scanning magnets, and in depth by the beam energy, and is swept across the treatment field, residing at each voxel the time required to deposit the prescribed dose. Typically, voxel size will be smaller than the beam size (by a factor of 2 or 3), to allow for some smoothing. The target could have as many as 10^5 voxels, so dose rates and dosimetry response times are extremely critical; dwell times at each voxel will be only a few 100 µs, and delivering the ±2% dose requires timing to even higher degrees of accuracy. Implications on accelerator performance can be seen immediately: spill structure can lead to unacceptable dose non-uniformity.

2 EXPERIENCE

Patients have been treated with heavy charged particles at three facilities to date: the Bevalac at Berkeley, USA, HIMAC in Chiba, Japan and GSI in Darmstadt, Germany.

2.1 Bevalac [5]

Between 1977 and 1992 a total of 433 patients received treatments with heavy-ion beams. Most of the treatments were with 670 MeV/amu neon, though several patients were treated with carbon, silicon and even argon beams. About half of the patients received their full treatments with heavy ions, the remainder received heavy ions as boosts for photon or light-ion treatments.

Two treatment rooms were available, both with horizontal beams. Patients were treated mainly in a sitting position, a special CT scanner, modified to scan seated patients, was installed to ensure accurate treatment planning. Initial beam delivery utilized the scattering system, a wobbler introduced in the 1980's improved beam utilization and quality. A scanning system was built, and one patient was treated with it just prior to shutdown of the facility. All treatments were of the "2-D" variety. Although the "3-D" range-stacking technique had been researched, and a suitable MLC built, this system was not developed in time for clinical implementation.

The use of radioactive beams for treatment verification was also pioneered at the Bevalac. ^{19}Ne beams were produced, purified and delivered to the treatment room, where patients located inside a PET camera were scanned to verify accuracy of the treatment plan. This was used specifically in the head-and-neck region where tissue inhomogeneities (air cavities, bone, soft tissue) can lead to difficulties in accurate determination of the beam range.

The Bevalac provided the basis for many of the subsequent developments in the field; the quite positive clinical results provided justification for further trials.

2.2 HIMAC [6,7]

In 1994, HIMAC in Chiba, Japan started clinical use; as of March 2000, 765 patients had been treated. Two 800 MeV/amu (10 T-m) synchrotrons separated vertically by 10 meters, are injected by a 6 MeV/amu RFQ, Alvarez DTL linac chain. Three ion sources, a PIG and two ECR sources provide ions up to Xe, though the main ion used for therapy is carbon at energies of 290, 350 and 400 MeV/amu. Three treatment rooms are used, one with a vertical beam, one with horizontal, and one with both horizontal and vertical beams. Beam delivery to date has used the 2-D system with wobbler magnets. 3-D treatments with range-stacking and a multi-leaf collimator will be started in the coming year [8].

A fourth treatment room is being commissioned, with a radioactive ^{11}C beam produced by passing the ^{12}C primary through a beryllium target and magnetically separating the ^{11}C. As observed at the Bevalac, a surprisingly high efficiency is possible: almost 1% of the primary beam can be converted, analyzed and delivered to the treatment area as ^{11}C. This allows for excellent intensities for PET imaging, and even sufficient dose rates for actual treatment with the radioactive species.

Noteworthy is the very extensive ancillary research program being conducted at this facility. During the day on week-days, both synchrotrons are used for treating patients. However, evenings, nights and weekends are available for research in an extensive experimental area, separate from the clinical irradiation rooms. Over 200 researchers from around the world conduct experiments in radiation biology and biophysics, space-effects research, materials sciences, nuclear physics and atomic physics. Three different ions are available essentially continuously, one from each synchrotron and a third in a low-energy area fed directly from the linac.

RF Knockout extraction: To address the requirement for good control over the beam spill, a new system of extraction [9,10] is now in clinical use. It employs excitation of the beam at its horizontal betatron frequency to cause growth, instead of pushing the tune into a natural resonance. As the separatrix remains fixed, horizontal beam emittance is very low, and the exit orbit parameters remain constant, improving beam stability. Amplitude of the exciting RF controls the extraction rate, with excellent dynamic range. Beam can be turned fully on or off in 1 ms. Beam extraction efficiency is very high, between 80 and 90%. To accommodate the spread in beam tunes, the exciting signal is frequency-modulated, typically over a 5 kHz range (out of fundamental frequencies in the ≈1 MHz range). At present a 770 Hz sawtooth modulation function is used. The normal spill structure frequencies at 50 and 100 Hz (seen with the original resonant-extraction system) are almost completely suppressed, replaced with a substantial component at 770 Hz. This structure frequency has no effect on the accuracy of dose delivery with systems currently in use.

Beam gating: Organ motion due to breathing can be a severe problem for accurate treatment delivery in most areas outside of the head and neck. Usually, 1-2 cm margins are added to the target volume to cover all changes in shape of the treatment area, but this includes substantial amounts of normal tissue. Beam gating is now used at HIMAC to mitigate this problem. By triggering extraction based on the location of sensors attached to the patient, beam can be delivered during the same times in each breathing cycle. Measurements indicate the ability to reduce added margins due to breathing motion to only a few mm. Treatment times are lengthened, but by no more than about a factor of 2. Beam that is not used during a flattop is decelerated and dumped at lower energies, thus substantially reducing radiation effects.

2.3 GSI [11,12,13]

GSI has completed treatments on 54 patients since 1997 with a highly sophisticated "pencil beam" scanning system requiring extraordinary control of all the parameters of the accelerator system. The carbon beam is delivered to the therapy room horizontally with a slight (few degree) vertical offset angle to allow the beam to miss the patient if the scanning magnets lose power. Treatments have all been in the head-and-neck area, where tissue inhomo-geneity, as well as close proximity of critical structures present the greatest challenges to radiotherapy. Clinical results have been very encouraging, showing good response in the target area, and a surprisingly low incidence of skin reactions. These results are attributable directly to the superb localization capabilities of the pencil-beam scanning system.

Several two-week blocks are dedicated to radiotherapy during each year of operation. Initially the entire complex was devoted to therapy during these blocks, but as more confidence is gained, some background experiments are being conducted between treatment of patients. Overall reliability of the accelerator complex has been outstanding.

Scanning system: The scanning system takes full control of all accelerator parameters during a treatment. A total of 256 "virtual machines" are available: full sets of tuning parameters to encompass a wide range of energies, intensities and beam-spot sizes; any one of these "machines" can be called forth for each pulse. In addition, extraction of the beam can be shut off within a few ms, either for normal completion when no more beam is required at this energy or on detection of any abnormal condition in the delivery process.

Voxel size is typically a 3 mm cube, and scanned spot size about 1 cm FWHM. Voxels are treated sequentially at each depth of the volume, with commands to the scanning magnets to move to the next voxel given when dose for the present voxel will be completed. This calculation is complex, as a significant portion of the dose for each voxel is delivered during the actual time the scanner is responding to the command to move to the next point. Inputs include the rate of motion, the distance to be traveled (which could be large in moving between rows in a volume with highly slanted edges), and rate of dose deposition. Typically, a voxel receives its required dose in less than 1 ms, so response of the monitoring and control systems must be extremely swift.

No active control over the spill is included at this time (except a full cutoff), and the system is sensitive to spill structure. At present, the intensity is kept low to minimize the effect of structure on dose accuracy. This does lengthen treatment times, and methods are being sought to improve spill control. One of these is the HIMAC extraction scheme, which has already under test. An innovation being tried uses a noise-generated frequency-modulation scheme which should eliminate the FM sawtooth structure seen by HIMAC.

Noteworthy is the complete absence of patient-specific hardware. Except for the immobilization mask, there are no compensators, collimators, or other beam-shaping devices, thus simplifying the setup for each patient.

PET imaging: PET imaging has been fully integrated [14]. ^{11}C is produced by fragmentation of the ^{12}C treatment beam as it passes through tissue on its way to the treatment point. The ^{11}C has essentially the same range as the primary ^{12}C, so stops very close to the actual stopping point of the treatment beam. Imaging the positron annihilation radiation gives a direct measure of the stopping point of the beam, and can verify that beam has actually reached the planned treatment volume. The amount of ^{11}C produced is adequate for useful images, and has in some cases shown deviations as high as 5 to 6 mm from the calculated range of the beam, errors arising from imprecise handling of inhomogeneities in the treatment planning programs. Overall accuracy in treatments is improved by implementing measured corrections.

3 NEW INITIATIVES

Based on the very successful results to date, a healthy growth in the field is taking place, with new initiatives in both Japan and Europe in various stages of planning and implementation.

3.1 *Hyogo Province, Japan* [15]

The Hyogo Hadron Therapy Center is now nearing completion at the Harima Science Garden City. With capabilities for both protons and carbon ions, this center has 6 treatment rooms and 7 treatment ports. Three rooms are dedicated to carbon, one with a horizontal beam, one vertical beam and one oblique at 45°. The proton rooms include two with full isocentric gantries and one with two ports, one for small fields (mainly for ocular work) one for large static fields. Availability of both protons and carbon will enable good clinical intercomparisons. Beam delivery systems are based on HIMAC's; the proton gantries were purchased commercially.

Installation of all technical systems is now complete, and commissioning is underway. Beam has been extracted from the synchrotron to date, and meets all the design goals. First patient is expected in the spring of 2001, and full clinical operation a year after this.

3.2 *Heidelberg* [16,17]

The current GSI therapy project is a collaborative effort, with GSI providing the technical facilities and the Heidelberg Clinic and DKFZ responsible for the actual clinical activities. The long-range plan has always been to establish a dedicated facility close to the clinical centers at Heidelberg. A serious design study has now been completed, and project plans are being put together. Prospects for funding appear excellent. The facility will have three treatment rooms, two with gantries capable of full-rigidity carbon beams, and one fixed beam room. Beams planned are protons, helium and carbon, with oxygen at shorter ranges. All components (including gantries) are designed to operate equally well over the wide range of ridigities needed for all these beams.

Injection linac consists of an RFQ – IH-DTL chain with final energy of 7 MeV/amu. Two ion sources will provide the ions; an ECR for carbon 4^+, and a second (probably a volume source) generating H_3^+ ions. These ions have the same rigidity as C^{4+} and so will pass through the linac without retuning. The 7 T-m synchrotron is multi-turn injected (≈15-20 turns). With a pulse every 3 seconds, planned ramp rate allows for a 2 second flattop, or 60% duty factor. Extraction will be either by the normal resonant system currently employed at GSI, or the RF knockout system.

The GSI pencil-beam scanning system will be used for all treatments. The gantries are relatively compact, maximum diameter is less than 15 meters, not much larger than those currently used for protons. Magnet sizes are much larger and the overall length of the gantries, at over 20 meters, is also substantially greater. Overall weight of the gantry is over 600 tons. One feature allowing reduction in gantry diameter has been integration of the scanning magnets into the last bend. The slow scanner is located upstream, requiring larger width in the last 90° magnet, and the fast scanner is downstream, in direct line with the patient. The stability and accuracy of this split-magnet system are being tested in one of the GSI beamlines in the near future.

3.3 *PIMMS* [18]

The PIMMS (Proton-Ion Medical Machine Study) has been a collaborative study between CERN, GSI (Germany), Med-AUSTRON (Austria), TERA (Italy) and Oncology 2000 (Czech Republic) aimed at developing the best possible design for a synchrotron-based medical treatment facility delivering protons and carbon ions, without consideration of cost or site. This four-year study has led to many innovative features in accelerator design, and to development of the "Riesenrad" gantry concept [19].

The driving parameter for the entire design has been generation of a smooth, easily-controllable spill, to enable efficient implementation of scanning systems. The extraction system chosen uses a betatron core to accelerate the beam into the 5/3 resonance. Implementing the Hardt condition [20] maximizes stability of the extracted beam. For best extraction control, beams should have low emittance and large momentum spread, thus single-turn injection is preferred, and the lattice selected, a FODOF configuration with the first focusing quad split, forms a long dispersionless straight. For reasons of adequate beam intensity, single-turn injection had to be rejected in favor of a carefully controlled multiturn scheme which preserves as much as possible the phase-space density of the incoming beam.

Two separate linacs are called for, injecting carbon at 7 MeV/amu and protons at 20 MeV. These energies were selected to ensure that the circulating proton and carbon beams would have the same emittance at extraction, so would appear essentially identical (except for different rigidities) to the transport and beam-delivery systems.

Of note in the high-energy transport lines are special units to adjust the spot size on the patient: a "phase shifter" which changes the horizontal spot size for the by adjusting the phase advance; and a "stepper" which adjusts vertical betatron functions without affecting the horizontal ones. A "rotator" matches beams with differing horizontal and vertical emittances to the rotating gantry.

The "Riesenrad" gantry has been developed during this study. Greatly simplifying beam transport into a single rotating 90° dipole, this concept places the treatment room on a movable platform that follows the magnet as it rotates through a 180° arc providing beams from vertical overhead through horizontal to vertical from below. Vertical and horizontal translations achieve a net circular trajectory for the platform. The reduction in the number of magnetic elements results in significant savings in power consumption, structural weight, and cost. In addition, the only heavy magnetic element, the 90° magnet, remains close to the axis of rotation, simplifying structural design.

3.4 Med-AUSTRON [21]

With a site already selected close to a hospital complex at Wiener Neustadt, south of Vienna, this medical facility has considerable support within the Austrian medical community and government circles. The PIMMS design will be used, with implementation in a phased approach as funding is made available. At this time no definite timetable is possible, but optimism is high that this project will come to fruition.

3.5 CNAO [22]

The Centro Nazionale di Adroterapia Oncologica, is the centerpiece of the TERA Foundation. Planned for a site in Milan, the current concept incorporates much of the PIMMS design, but prefers the single injector and gantry concepts proposed for the Heidelberg project. Considerable detailed design and engineering work has been completed, with prototyping already underway of critical accelerator components. Interest in the project is extremely high, and project leaders are quite optimistic that site selection and funding plans can be worked out in the near future to enable an early start to construction.

4 SUMMARY

The field of therapy with light ions is maturing rapidly. Clinical experience has been excellent, and technologies have developed sufficiently to enable implementation in clinical settings. Several different paths to optimization of clinical accelerators, beam delivery and isocentric delivery have emerged, providing a variety of choices for designs. In addition to the two facilities operating today, several new facilities are coming on line, or are in serious planning stages. There is still much work to do, particularly in the area of spill structure and control. The new concepts from Japan and PIMMS need further tests and validation to ensure smooth implementation.

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