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# Medical Applications of Nuclear Physics and Heavy-Ion Beams*

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**Abstract**

Isotopes and accelerators, hallmarks of nuclear physics, are finding increasingly sophisticated and effective applications in the medical field. Diagnostic and therapeutic uses of radioisotopes are now a $10B/yr business worldwide, with over 10 million procedures and patient studies performed every year. This paper will discuss the use of isotopes for these applications. In addition, beams of protons and heavy ions are being more and more widely used clinically for treatment of malignancies. To be discussed here as well will be the rationale and techniques associated with charged-particle therapy, and the progress in implementation and optimization of these technologies for clinical use.

## 1. NUCLEAR MEDICINE

Radiation from decay of unstable nuclei is being routinely applied in diagnostic and therapeutic medical procedures[1,2,3]. The microscopic amount of material involved allows for chemical non-invasiveness in host tissue, as well as flexibility in bonding to tracer compounds that can deliver the radioisotopes to the desired area of the body. Perhaps the single most important area of impact has been on functional imaging: by labeling material such as deoxyglucose, a "fuel" used by cells, radioactivity will concentrate in tissues based on the amount of sugar metabolism. By identifying areas of reduced activity, such as heart muscle damage following a heart attack, or Alzheimer's disease effect on brain function; or increased activity in metastatic tumor growth, clinicians can obtain data not available by other techniques and develop appropriate treatment strategies. The damaging characteristics of highly-ionizing, short range radiation (alpha, low-energy beta) is used for therapeutic treatments, either by implantation of metallic "seeds" or by labeled pharmaceuticals tailored to seek out the desired treatment site. In all, nuclear techniques are now a mainstream element of today's medical practice, and will continue to grow as technologies are developed to improve efficiency of production and delivery of isotopes.

### 1.1. Basic Considerations

The diversity of halflives and radiation characteristics of known isotopes offers a very wide range of candidates for practical applications. Optimizing each use requires matching desired

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properties with available isotopes. Therapeutic and diagnostic applications have substantially different requirements for isotopes, each aimed at maximizing clinical effectiveness while keeping to a minimum the radiation not directly involved with the particular procedure.

### 1.1.1 Nuclear characteristics

Diagnostic applications require radiation that can penetrate from the site of the decaying nucleus, and be registered in detectors positioned outside the patient. For this, gamma or x-rays of energies from about 50 keV to a few hundred keV are best suited. Higher energies, while absorbed less in the body, are also less-efficiently detected by the highly-segmented detectors required for good image resolution. Positron annihilation radiation (511 keV) represents about the upper limit, which is widely used because of the colinearity of the two gamma rays that affords excellent positioning accuracy. Alpha-emitting isotopes, or those with substantial amounts of low-energy gammas or betas are less desirable for diagnostic applications because this radiation contributes to patient dose without adding value to the diagnostic procedure.

Isotopes best suited for therapeutic applications, on the other hand, will exhibit highly-ionizing, short range radiation: alphas, low-energy betas or photons, with a minimum of higher-energy components. This keeps the radiation dose localized in close proximity to the isotope location, and facilitates the tailoring of the radiation dose to the actual desired treatment volume.

Both types of applications share requirements for optimal halflife, favorable chemical properties, ease of production and transport to use site, and cost-effectiveness. The halflife must be long enough to ensure that sufficient quantities remain following production, transportation and chemical preparation prior to administration to the patient. But at the same time the residual activity in the body at the end of the procedure must decay as quickly as possible, as the follow-on radiation burden to the patient provides no clinical benefit.

### 1.1.2 Chemical properties

Once administered, the activity must quickly and selectively reach the desired target area within the body. This requires chemical processing into a bioactive molecular form, or in some therapeutic applications, direct placement of the isotope by surgical implantation of activated “seeds,” often referred to as “brachytherapy.” Chemical processing usually involves replacement of a constituent of the molecule with the radioactive isotope, such as tritium for hydrogen, $^{11}C$ for $^{12}C$, $^{15}O$ for $^{16}O$, $^{18}F$ for $^{19}F$ or as a chemical analog for other halogens or even $OH^-$. In some cases, such as many metallic species, where normal isotopic substitution is not possible, molecular “cages” or chelates are used to trap the isotope for transport to the desired site. The best example here is $^{99m}Tc$, one of the most widely used single-photon imaging isotopes.

### 1.1.3 Production considerations

Radioisotopes for medical use are produced by several different techniques. Neutron activation via reactors, or chemical separation from spent nuclear fuel is widely used, again the prime isotope generated by this means is $^{99}Mo$, parent of $^{99m}Tc$. High-current cyclotrons with energies up to around 30 MeV produce a wide range of isotopes via (p,xn) as well as (d,xn) and some ($\alpha$,xn). These relatively large and complex machines, as well as the extensive equipment for remote handling of the intense radioactivity generated, typically are located

close to major distribution centers that can deliver the isotopes to end-use sites very rapidly. Much smaller accelerators, with energies between 7 and 18 MeV, are also installed directly in hospitals or other end-use sites, and are used for producing very short-lived isotopes (e.g. $^{11}C$, $^{18}F$) usually for PET studies. These highly compact, self-shielded and fully automated systems reduce to an absolute minimum the delay time between production and administration. Typically, chemical processing is accomplished automatically and sometimes continuously in close proximity to the target itself, with rapid transport to the PET imaging area.

One other production method widely used is the so-called "generator" system. A relatively long-lived species is made at a large center, and is shipped to the end-use site. This long-lived parent decays to a shorter-lived daughter, which is the isotope actually used in the medical procedures. The daughter is "milked" from the parent by chemical or physical techniques, samples being prepared directly as needed for procedures. The aforementioned $^{99}Mo$ (67 hour) – $^{99m}Tc$ (6 hour) generator is used in about 70% of all nuclear medicine studies today; others are $^{68}Ge$ (287 days) – $^{68}Ga$ (68 minutes), a $\beta^+$ emitter used for PET calibrations and studies; and $^{82}Sr$ (25 days) – $^{82}Rb$ (1.2 minutes), also a $\beta^+$ emitter used for PET heart studies.

It should be mentioned that research isotopes are also produced by higher-energy proton accelerators at several large laboratories: Brookhaven (BLIP), Los Alamos (LANSCE) and TRIUMF, but the small quantities produced, and the lack of continuous availability from such sources limits their clinical usefulness.

Steady, reliable access to an isotope is perhaps the single most important factor in its effective clinical use. As an example, one can point to the chaos that ensued a few years ago when a Canadian reactor had to be shut down for emergency repairs, causing a significant disruption in the flow of $^{99}Mo$.

### 1.2. Diagnostic techniques

Instrumentation capable of imaging the concentration of activity with good spatial resolution is key for effective diagnostic application. The Anger Camera[4], developed in the late 1950's was the first device to meet these requirements. It consists of a large array of NaI detectors with a honeycomb high-Z collimator to limit angular acceptance. Planar projection images with resolution of about 1 cm were obtained.

A natural evolution was SPECT[5], or Single Photon Emission Computerized Tomography. The Anger Camera is mounted on a rotating fixture capable of collecting planar images at a number of different angles around the patient, then tomographic reconstruction algorithms are applied to obtain a more detailed 3-D map of activity distribution. This technique is used today for a large fraction of all nuclear medicine procedures, using isotopes such as $^{99m}Tc$ (140 keV gamma) for a wide variety of sites, and $^{201}Tl$ (70 keV x-ray) for heart studies. The popularity of the technique arises from easy availability of isotopes, and relatively low cost of diagnostic instrumentation.

PET[6] (Positron Emission Tomography) is widely used for functional imaging studies. Making use of

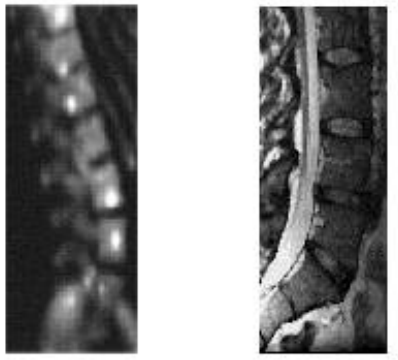


Figure 1: **Vertebrae and spinal cord images.** PET image shows metastatic tumors, from higher uptake of FDG

the colinearity of annihilation radiation, this technique has intrinsically much better resolution than SPECT, as well as providing quantitative information about isotope uptake. Instrumentation is complex: PET rings now have over 600 BGO detectors with sophisticated electronics to track coincidences and suppress Compton events in adjacent detectors. Resolution in today's PET instrumentation approaches the theoretical limit of around 2 mm, determined largely by positron range prior to annihilation.

The study shown in Figure 1 compares a PET image of vertebral bodies with an MRI image of the same area. While the MRI image shows much more detail at higher resolution, the PET image indicates the presence of metastatic tumor not visible in the MRI picture. Tumor tissue, by virtue of higher metabolic activity, exhibits substantially higher uptake of the $^{18}$F tagged deoxyglucose (FDG) "fuel."

New uses of PET are being continually developed; an interesting new application is in tagging of markers that can indicate expression of genetic material introduced into tissue[7].

### 1.3. Therapeutic uses

The tumor selectivity of tagged molecules can be used for delivering a therapeutic radiation dose to treatment sites[8]. $^{188}$Re, $^{117m}$Sn, $^{89}$Sr are used for treating metastatic sites, and bone lesions as well as for palliation and pain relief; $^{131}$I is used extensively for thyroid diagnostics and treatments. $^{103}$Pd is produced by (p,n) on metallic Rh targets, the resulting "seeds," with no chemical processing, are surgically implanted for prostate tumor therapy. Similar "seeds" or "plaques" of $^{145}$Sm are used for treatment of eye tumors. These implants usually are removed following administration of the desired dose.

### 1.4. BNCT (Boron Neutron Capture Therapy)

BNCT[9], while not employing radioisotopes, nonetheless involves nuclear processes. Enrico Fermi suggested in the 1930's that boron could be attached to a tumor-seeking compound, and following administration of the pharmaceutical to the patient the area could be flooded with thermal neutrons. The disintegration of the boron nuclei following neutron capture would cause an enhancement of the radiation dose in the boron-rich regions, to clinical advantage. The technique was viewed as a potential treatment for glioblastoma[10], a very stubborn brain tumor that responds poorly to all known therapeutic modalities.

Initial trials in the 1950's using reactors at MIT and Brookhaven were not successful. Analysis indicated several possible reasons for the failures: imperfect selectivity of the pharmaceuticals leading to enhanced damage to normal tissue; toxicity of the pharmaceuticals which limited dosage that could be administered to the patient; and non-optimal neutron energy spectrum – the thermal neutrons were absorbed more readily in shallow layers, causing more damage there than at the deeper site of the tumor.

Work has continued with investigation of more suitable pharmaceuticals, and with the development of epithermal (keV) neutron beams that become thermalized at the appropriate depth. A new set of trials was undertaken at MIT and BNL, but has recently been suspended as well because of less-than-favorable results. Microscopic examination of sites treated, however, indicate that the treatments can be effective in killing the tumor – a significant advance for glioblastoma – however patient failures continue to occur, largely because of complications resulting from the treatment. One possible factor: while new pharmaceuticals better seek out the tumor, concentrations in the blood vessels remain too high, resulting in radiation damage to vessel walls often leading to hemorrhaging.

It can be concluded that BNCT can be an effective technique for treating glioblastoma, if the technique can be perfected to where normal tissue damage can be controlled to acceptable levels. The directions to be taken are in continued search for the appropriate pharmaceutical, and in better definition and control of the neutron beam.

## 2. HADRON BEAMS

Proton and ion beams provide significant advantages for delivering dose specifically to a desired treatment volume, by virtue of the Bragg curve[11]. This intrinsic advantage is seen in Figure 2. As the maximum of ionization occurs close to the stopping point of the charged particle, adjusting beam parameters so particles stop inside a tumor will provide a significantly enhanced dose to the tumor over normal tissue being traversed before the beam stops.

Although the concept is very straightforward, achieving its full therapeutic potential has been very difficult. Precise definition of the target volume has only become possible with the advent of CT and MRI imaging, that now allow accurate treatment planning; and techniques for the precise placement of beam in an irregular treatment volume are only now becoming available for clinical implementation.

### 2.1 Developing clinical experience with protons

Treatment with proton beams began in the 1950's, at nuclear physics research centers in Berkeley, Boston and Uppsala, with slow, steady expansion to encompass over 20 centers around the world offering protons for therapy[12]. A total of over 30,000 patients have been treated to date, indicating a high degree of maturity for this modality.

The first treatments employed "plateau" irradiations, using high-energy beams that exited the distal side of the patient, and placing the small field (e.g. pituitary gland) at a center of rotation to enhance the dose. These treatments made use of the stiffness of the beams rather than the Bragg peak itself, lacking accurate electron-density information to calculate the exact stopping point of the beam. First stopping-beam therapy occurred for ocular treatments: the short range and homogeneity of the tissue traversed enabled accurate assessment of stopping points.

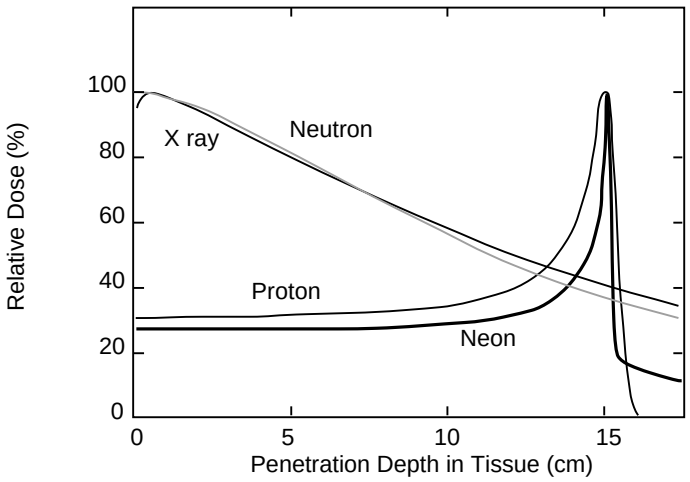


Figure 2: **Comparative depth dose profiles.** Fast neutron (≈60 MeV) and X-ray (≈10 MeV) distributions follow exponential curve, Protons and heavier charged-particles follow 1/E Bragg curve to end of range. Proton peak is broader due to multiple-scattering and range straggling. Neon tail is result of nuclear fragmentation reactions.

Precision Bragg-peak therapy became possible with development of CT technology, and is now the principal application of this modality.

Loma Linda University became the first center built in a hospital environment exclusively for proton therapy[13]. Commissioned in 1990,

over 5000 patients have been treated to date in this facility offering three fully-isocentric gantries and two fixed-beam rooms. A new center at the Massachusetts General Hospital in Boston is being commissioned[14], and several other major medical centers in the US are actively pursuing acquisition of this technology through the now-emerging group of commercial vendors capable of supplying it.

Considerable proton-therapy activity is taking place in Japan[15]: a treatment program at the KEK PS-Booster, ongoing now for over 15 years, will be phased out in favor of a new dedicated synchrotron facility at the University of Tsukuba. A hospital-based facility in Kashiwa has been treating now for over a year, and three new clinical facilities are approaching completion.

The center of proton-therapy activity in Europe now resides at PSI[16] in Villigen, Switzerland, and at Nice and Orsay in France[17]. While these programs are relatively small to date, there is growing interest in their expansion and further development of new facilities.

Proton therapy is gaining popularity by virtue of the advantages of Bragg peak therapy, and by the relatively lower-cost of acquisition of the capability. In the US, economic models now exist indicating that a proton-therapy center can be profitable even without any government funding for construction or operations subsidy.

As will be seen below, protons do not represent the apex of charged-particle application for therapy; ultimately it would be desirable to select whatever ion is most suitable for each treatment site without limiting oneself to only protons.

## 2.2 Rationale for heavier ions

Two properties of ions heavier than protons make them potentially better for therapy: stiffer trajectories leading to sharper dose-localization; and greater ionization power which translates into a higher degree of biological damage[18].

### 2.2.1 Physical characteristics

Multiple scattering and range straggling significantly affect the sharpness of the stopping point of protons, as can be seen by comparing the proton and neon Bragg curves in Figure 2. A thin parallel proton beam of one or two mm width penetrating 23 cm into a patient will spread to over 20 mm at end of range. Figure 3 shows this, and relative scattering and range straggling for different ions; clearly, carbon and heavier ions retain substantially better edge-definition to the end of their range. Nuclear reactions contribute to the dose, though in a minimal way. Peripheral reactions generate lighter "spectator" fragments that generally travel farther than the primary beam, leading

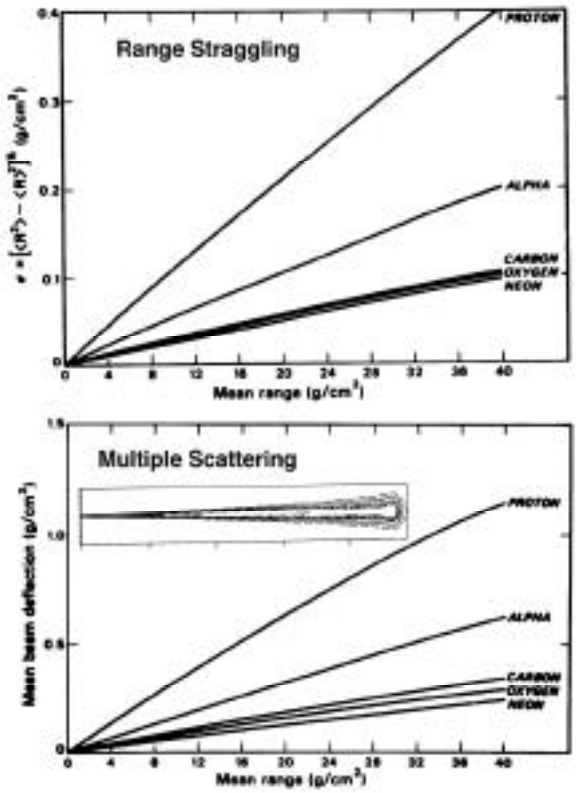


Figure 3. **Multiple-scattering, range straggling curves for protons and ions.** Inset demonstrates spreading of 23 cm-range proton pencil beam.

to the "tail" on the neon Bragg curve in Figure 2. Note, protons have no such "spectator" fragments, and hence no tail. As dose varies as $Z^2$, dose per fragment is of less importance than that from primary ions.

This fragmentation process can be turned to an advantage for ions, in that a significant portion of the fragments produced are positron emitters, and can be used for PET imaging of the treatment area[19].

### 2.2.2 Biological characteristics

Energy deposition, or ionization density along a particle track scales as $Z^2$ of the ion. Biological damage is caused by the electrons (delta rays) forming this track, which break molecular bonds, and is related to the "LET" (Linear Energy Transfer, or differential energy absorbed by material in contrast to dE/dx, energy lost by the particle). For "low-LET" radiation (e.g. x-rays, protons) the ionization density is sparse enough that the effectiveness of radiation damage is dominated by repair mechanisms; sufficient intact structures surround areas of damage to provide adequate templates for repair. Free radicals, and other factors impacting repair processes will play important roles. On the other hand, "high-LET" radiation will cause extensive damage that may not be so easily repaired. Normally radio-resistant tumors can be more successfully treated in this regime. Note, however, that beyond a certain point the energy available in a track is no longer effective, a situation that could be described as "overkill." No clear threshold can be drawn, but it is generally accepted that ions heavier than argon would never be suitable for clinical use. This question will be discussed further below.

### 2.2.3 Selection of the "ideal" ion

LET varies along the Bragg curve, reaching a maximum at the end of range. As the whole curve scales as $Z^2$, most desirable would be to find the ion in which the entrance ("plateau") dose is "low-LET" affording minimum damage to normal tissue, while the stopping ("peak") region were in the "high-LET" region. In actuality, there is no clear dividing line between "low" and "high" LET regions, and the level of damage is highly dependent on tissue type, state of blood flow to these tissues, and other factors. Initial evaluations based on extensive radiobiological work at Berkeley in the late 1970's, indicated that neon ions (Z=10) would be the best to use, and over 400 patients were treated with neon at the Bevalac through 1992. Subsequent experimental and modeling work has led researchers in Germany and Japan to select carbon (Z=6) for their clinical trials, as a way of reducing normal tissue effects without compromising the gains of high LET in the stopping region.

There really is no "ideal" ion for all cases, however. Some tumors might respond better to beams with higher ionization power, and heavier ions may be better suited if these tumors are located close to the skin where little normal tissue would be involved. Others may be best treated with lighter ions, such as protons, where dose localization may not be of absolutely critical importance, or where there is a desire to keep to an absolute minimum the involvement of normal tissue, such as is the case with pediatric patients.

## 2.3 Facility considerations for hadron therapy

Once the ion species have been selected, one can generate specifications for the accelerator and beam-delivery systems needed[20].

### 2.3.1 Range, energy

Sufficient energy is needed to reach the deepest point of a volume to be treated. The accepted maximum range is 30 cm in tissue, which translates to a top energy of around 250 MeV for protons, or 425 MeV/amu for carbon. Few tumors are 30 cm deep, however most treatments involve several entry ports requiring access from different angles and in some cases using every bit of available range. Variable energy is important, to treat shallower tumors and to place stopping particles at shallower depths in the treatment volume. This energy variation can be done by changing the extraction parameters for a synchrotron (which should be done on a pulse-by-pulse basis to be most effective), or by adding variable degraders to the beam after it has been extracted. This method is less desirable, because of beam loss due to nuclear reactions (adding to neutron backgrounds, incidentally), as well as loss of beam quality due to scattering and straggling. (Note that energy-degrading systems for protons have been developed that are quite effective – though do produce a lot of neutrons – and enable the use of fixed-energy cyclotrons for clinical therapy.)

### 2.3.2 Intensity, dose rate

Accepted as the required dose rate is that which will complete treatment of a volume of 20 x 20 cm by 10 cm thick, to a dose of 2 gray, in less than 1 minute. Particle fluxes of $\approx 1 \times 10^{10}$ protons per second, or $\approx 3 \times 10^{8}$ carbon ions per second are needed. These are particles actually delivered to the treatment volume; extracted current capability should be substantially higher (x2 to x5) to account for collimation losses and other measures required to accurately deliver the dose to the patient.

### 2.3.3 Dose accuracy, beam delivery

Response of tissue to radiation is highly non-linear. Up to a critical threshold there is very little response, but the survival rate goes from 100% to zero over a very narrow range of dose. Hence, it is very important to control with a high degree of accuracy the dose actually delivered to each element of the treatment field, to achieve the desired response to the tumor and minimize the effect on normal tissue. The specified accuracy is ±2%. Note, each volume element ("voxel") of the target receives dose both from particles stopped within it as well as from particles that pass through going to deeper elements. Treatment planning codes unfold these factors, including the different biological response to traversing and stopping particles, and specify the entry port orientations and the number of particles to be stopped in each voxel. The delivery system must be capable of executing this plan, to the specified accuracy. Note the distinction between "accuracy" and "uniformity," an optimized plan will not have uniform particle distributions in all areas of the treatment field.

#### *2-D delivery*

The simplest "passive" delivery systems involve passing the beam through a complex scattering system that produces a flat radiation field at the patient site. The basic gaussian scattering distribution is modified by one of several means – e.g. radially-varying foil thickness – to ensure flatness over the treatment field; good field sizes up to 30 cm diameter can be obtained by these techniques. For heavier, more rigid beams, scattering is less effective for producing large transverse fields, and magnetic "wobbling" systems are used. These can either paint concentric circles (by varying the amplitude of a sinusoidally-excited orthogonal pair of magnets), or a rectangular field, by rastering "fast" and "slow" scanning magnets. The

beam spot size that is swept across the field is usually fairly large (few cm FWHM), which helps smooth out irregularities, but still a reasonable time-uniformity of the beam spill is required to ensure a flat field distribution.

In both cases, range 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 by the shape of the walls of the groove. Families of such filters are used to obtain fields with different SOBP widths, each treatment will employ the filter which spreads the stopping points to cover the thickest portion of the treatment volume.

Such delivery systems produce treatment fields with basically cylindrical symmetry; constant range modulation over the whole field. As seen in Figure 4a a collimator is used to shape the transverse dimension, and a "bolus compensator" is placed in front of the patient to shape the deepest (most "distal") end of the treatment field, to avoid critical structures beyond the edge of the tumor for instance. This "2-D" technique will involve normal tissue to the full treatment dose, and lacks the ability to tailor dose for individual voxels. However, it is relatively simple to apply, and has been the workhorse for most therapy programs to date.

*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 a "multi-leaf collimator," and is demonstrated in Figure 4b. The leaf collimator, two sets of stacked sheets 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.

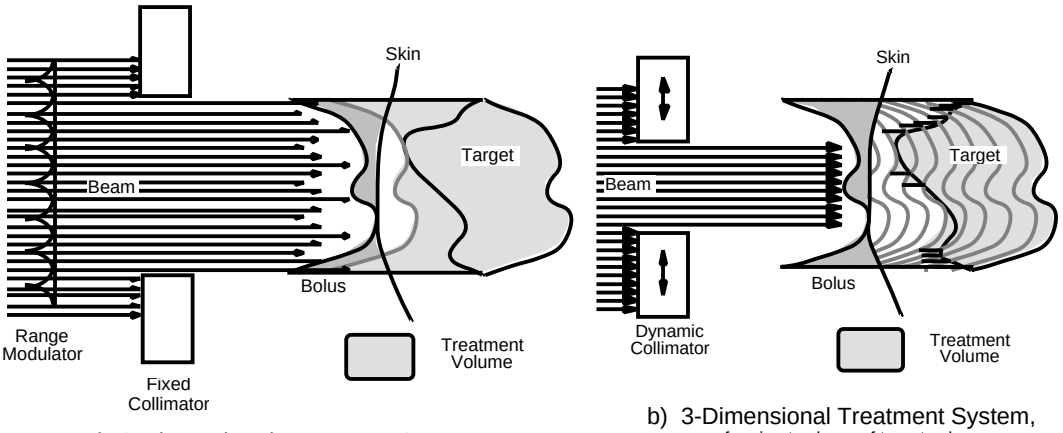


Figure 4. **Beam delivery system schematics.** a) Classical "passive" system uses range-modulator "filter" to spread stopping point of particles over maximum thickness of tumor, static collimator shapes field for largest lateral extent of tumor. b) Dynamic collimator shapes field for target volume at each narrow energy slice selected. This "range-stacking" technique, and pencil-beam scanning are two methods of achieving true conformation of dose to irregular target volumes.

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 moved 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. A typical target could have as many as $10^5$ or $10^6$ 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. For instance, time-structure in a synchrotron spill can lead to unacceptable dose non-uniformity.

#### 2.3.4 Safety, reliability

An accelerator system operating in a clinical environment is expected to have in excess of 95% reliability; 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, in addition to beam time for calibrations and Quality Assurance checks.

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.

### 2.4 Heavy-Ion Therapy: Experience to Date

Patients have been treated with carbon or heavier ions at three facilities to date: the Bevalac at Berkeley, USA; HIMAC in Chiba, Japan; and GSI in Darmstadt, Germany.

#### 2.4.1 Bevalac

Between 1977 and 1992 a total of 433 patients received treatments with heavy-ion beams at the Bevalac[21,22]. Most of the treatments were with 670 MeV/amu neon, though some 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 helium-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 Bevalac. All treatments were of the “2-D” variety. Although the range-stacking technique had been researched, and a suitable multi-leaf collimator 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[23]. $^{19}$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 substantial tissue inhomogeneities (air cavities, bone as well as 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[24], as well as the strong justification to continue research with ion beams, owing to the excellent clinical results obtained.

### 2.4.2 HIMAC

In 1994, HIMAC[25] in Chiba, Japan started clinical operations; as of March 2000, 745 patients had been treated. This facility consists of two 800 MeV/amu (10 T-m) synchrotrons separated vertically by 10 meters, injected by a 6 MeV/amu linac chain. Three ion sources provide ions up to Xe, though the main ion used for therapy is carbon. 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 been 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[26].

A fourth treatment room is being commissioned, for exclusive use with radioactive $^{11}C$, for both diagnostic, as well as treatment of small fields. The $^{11}C$ is produced in an external beryllium target, and magnetically separated from the primary. As observed at the Bevalac, a very high degree of 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 as stated, even sufficient dose rates for actual treatment with the radioactive species.

Several innovative concepts developed at HIMAC deserve mention. A beam-gating system to compensate for patient breathing motion has been developed, allowing for accurate treatment delivery in the thoracic region by using sensors mounted on the patient's chest to enable beam extraction at the same point each breathing cycle[27]. A new system for extracting beam from the synchrotron by exciting the beam at its natural betatron frequency has demonstrated easier control, less spill structure and better efficiency[28]. This new technique could have widespread application for slow extraction from synchrotrons, potentially benefiting many fields of research.

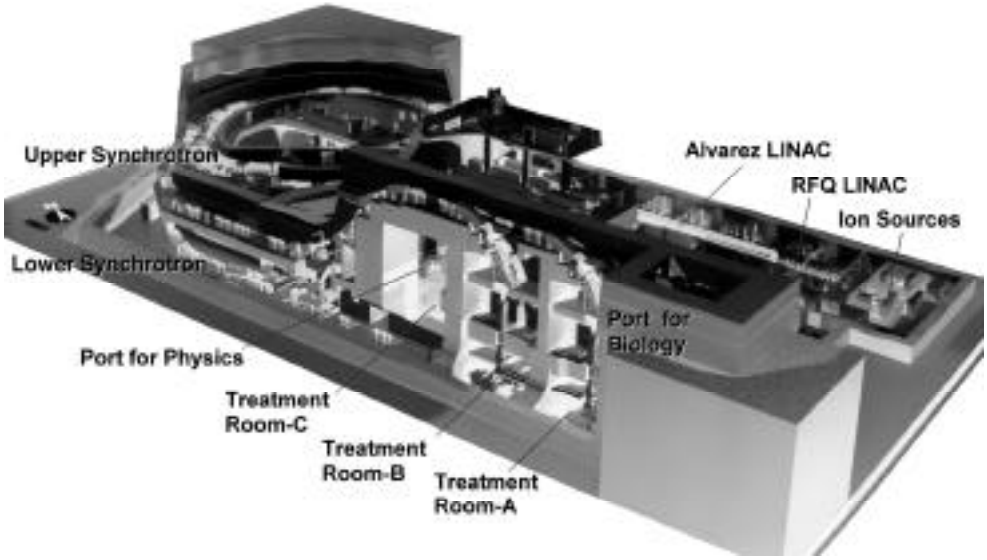


Figure 5. **Schematic of HIMAC**
Three treatment rooms: fixed horizontal and vertical beams

Noteworthy is the very extensive ancillary user program being conducted at HIMAC. During week-day hours, both synchrotrons are used for treating patients. However, evening and night hours, as well as all weekends, are available for research in an extensive experimental area, separate from the clinical irradiation rooms. Active programs in radiation biology and biophysics, space-effects research, materials sciences, nuclear physics and atomic physics are being conducted. The external research community numbers almost 200 and includes researchers from US and other countries in addition to local programs from Osaka, RIKEN and other institutions. Three different ions are available essentially continuously, one from each synchrotron and a third in a low-energy area fed directly from the linac.

### 2.4.3 GSI

GSI started clinical operations in 1997[29], and has completed treatments on 72 patients using carbon ions and a highly-sophisticated pencil-beam scanning system[30]. Treatments have all been in the head-and-neck area, where the large degree of tissue inhomogeneity, and close proximity of critical structures presents great challenges to precision radiotherapy. To date results have been very good even considering the very short followup time, showing good response in the actual target area, and a surprisingly low incidence of skin reactions. These results are attributable directly to the superb dose-control capabilities of the pencil-beam scanning system.

Several three-week blocks are dedicated to radiotherapy during each year of operation, accounting for the low number of patients treated. The mission of this program, however, is primarily a technology demonstration of highly-advanced accelerator-control and beam-delivery techniques rather than actual clinical research. Once proven, and accepted by the medical community, a dedicated facility is planned at Heidelberg to carry out an extensive clinical research program. To date, the program has been an outstanding success; the superiority of pencil-beam scanning well demonstrated, and overall reliability of the delivery systems and accelerator complex quite exceptional. The medical team head states the GSI system is more reliable than the clinical machines in his department at Heidelberg.

*Scanning system*

The scanning system takes full control of all accelerator parameters during a treatment. A menu of 256 “virtual machines” is 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 milliseconds, either for normal completion or upon detection of any abnormal condition in the delivery process. The full treatment is delivered with no operator intervention.

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 by predicting 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 100 μs, so response of the monitoring and control systems must be extremely swift. An active display of progress of the treatment is shown in Figure 6. All of the slices to be treated are shown in the background, the slice

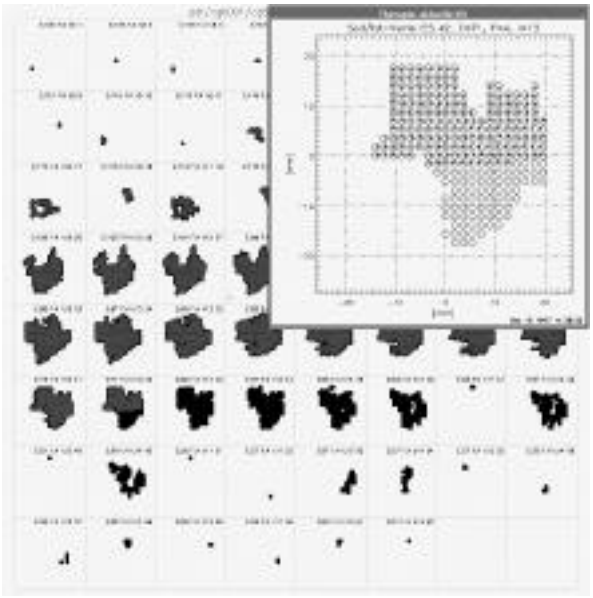

Figure 6. **Screen-shot during treatment with GSI pencil-beam scanning system.** Background squares depict field shape at each depth, gray slices have been treated. Inset is slice currently under treatment, black dots represent center of beam in each voxel. Circles are 1 mm dia, actual beam-spot is 3 mm dia.

currently being treated is blown up and progress of the spot across the field is shown. The slight offset within each circle shows the deviation of the beam from dead center for that voxel, the diameter of the circle being 1 mm.

No active control over the beam intensity delivered is included at this time, so the system is sensitive to spill structure. At present, the intensity is kept lower than what is fully available to minimize the effect of temporal inhomogeneity in the beam. This does lengthen treatment times, and methods are being sought to improve spill control to mitigate this issue. Specifically, the new HIMAC extraction scheme is being investigated.

*PET imaging*

PET imaging has been fully integrated into the treatment methodology, using $^{11}C$ produced by fragmentation of the $^{12}C$ treatment beam as it passes through tissue on its way to the treatment point[31]. 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 then 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, though lower than what could be produced with an external target, is adequate for producing useful images and has the advantage of monitoring the actual treatment. In some cases deviations as high as 5 to 6 mm in the calculated range of the beam have been observed. Measurements conducted during early fractions have allowed modification of the treatment plans to correct these errors to ensure accurate overall treatments.

## 2.5. New Initiatives

As a result of 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.

### 2.5.1. Hyogo Province, Japan

The Hyogo Hadron Therapy Center[32] is now nearing completion at the Harima Science Garden City, not far from Kyoto. With capabilities for both protons and carbon ions, this center has 6 treatment rooms and 7 actual 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 at the same facility will enable good clinical intercomparisons, and refinement of treatment techniques applicable to each ion.

Technology and beam delivery systems are based on those developed at HIMAC, while the proton gantries have been acquired from one of the commercial vendors now supplying these for routine use at proton facilities around the world.

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.

### 2.5.2 Heidelberg

Based on the success of the GSI project, plans are progressing for the dedicated facility in close proximity to the Heidelberg Clinic and the DKFZ[33,34]. Designs are quite well along, and prospects for funding appear excellent. Ground-breaking is expected within a year.

The facility will have three treatment rooms, two with gantries capable of the full-rigidity carbon beams, and one fixed beam room. Beams planned are protons, helium and carbon, with capabilities for oxygen at shorter ranges. All components (including gantries) are designed to operate equally well over the wide variation of ridigities between these beams, the same rooms being used for both proton and carbon treatments.

A straightforward synchrotron design has been developed, with close attention to beam quality and interfacing with the pencil-beam scanning system for all beams. Injected at 7 MeV/amu, the 7 T-m ring cycles at about 1/3 Hz, allowing almost a 2-second flattop for beam extraction.

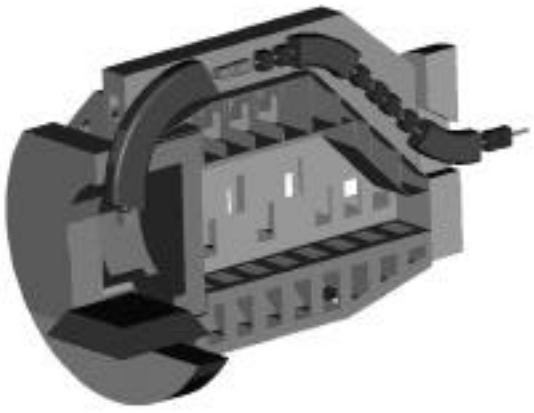

Figure 7.
**Model of carbon-ion gantry for Heidelberg**.
Diameter is 15 meters, total weight ≈700 tons.

The gantries are relatively compact, maximum diameter is less than 15 meters, not that much larger than those currently used for protons. Magnet sizes are, however, much larger and the overall length of the gantries, at somewhat over 20 meters, is also substantially greater. Overall weight of the gantry, with the very significant steel supporting structure, is around 700 tons. Figure 7 shows the layout for these gantries. One feature allowing reduction in gantry diameter has been moving the scanning magnets upstream of the last bend, at the price of a much larger magnet gap and width to allow for

expanding beam throughout the bend. A prototype of this 90° magnet is being designed and built now, and the scanning optics and accuracy will be tested on the GSI floor in the near future.

### 2.5.3 PIMMS (Proton-Ion Medical Machine Study)

The PIMMS[35] has been a collaborative study sponsored by 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, as well as to development of the "Riesenrad" gantry concept[36].

The driving parameter for the entire design has been producing a smooth, easily-controllable spill, to enable efficient implementation of scanning systems. Lattice parameters – as well as design decisions for all other machine systems – are driven by most efficient matching to the specified extraction system, one based on the betatron-core system employed at Saturne. Optimization for both protons and carbon drove the team to specifying two separate injection linacs, with multiturn injection at 7 MeV/amu for carbon and 20 MeV for protons.

The "Riesenrad" gantry reduces the beam transport system into a single rotating 90° dipole, with the treatment room placed on a movable platform which follows the magnet as it rotates through a 180° arc from vertical overhead through horizontal to vertical from below. The platform motion is accomplished by vertical and horizontal translations to achieve a net circular trajectory, much like that of a Ferris wheel (hence the name). The simplification in beam transport reduces cost and power consumption, as well as structural costs as the only heavy magnetic element, the 90° magnet, remains close to the axis of rotation. Shielded vault volume is substantially reduced as well. Alignment between the magnet (beam) and room (patient) coordinate systems is accomplished through laser-tracking technology; sub-millimeter precision is anticipated. This new concept bears serious consideration, though a substantial marketing program will be needed to convince a medical community that is used to having all the beam hardware rotate around a stationary patient.

### 2.5.4 Other European projects

The PIMMS design has become the technical basis for several new initiatives in Europe, described below.

#### *Med-AUSTRON*

With a site already selected close to a hospital complex at Wiener Neustadt, south of Vienna, the Med-AUSTRON project[37] 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 available, but optimism is high that this project will come to fruition.

#### *CNAO*

The Centro Nazionale di Adroterapia Oncologica, is the centerpiece of Italy's TERA Foundation[38]. Planned for a site in or in close proximity to 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.

*Lyon*

Strong interest is being expressed for a clinical facility at the Universite Claude Bernard in Lyon with capabilities for carbon and proton ions[39]. The PIMMS design is being adopted as a baseline model. Teams are working through siting, funding, and technical requirements issues, with encouragement from local and federal governments. A recent well-attended workshop points to an enthusiastic and supportive medical community in France behind such an undertaking.

## 3. Summary

Nuclear physics is having a strong impact on medicine: in the application of radioisotopes directly, as well as accelerators and other research instrumentation. Imaging with radioisotopes is economical and effective, and is continually developing both in better resolution as well as new fields of application. Clinical experience to date with heavy-ion beams has been excellent, and is providing impetus for significant growth in the field. In addition to the two ion-beam facilities operating today, several new facilities are coming on line or are in serious planning stages, and interest is being expressed at several other sites for implementation of ion-beam therapy. Several different paths to optimization of clinical accelerators, beam delivery and isocentric delivery have been developed, providing a variety of choices for designs for the new facilities. There is still a lot of work to do in all these areas, with opportunities for members of the nuclear physics, accelerator and medical communities to work synergistically towards effective development of these concepts for the benefit of humanity.

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