LBL-36229
UC-408

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To be published as a chapter in *Textbook of Radiation Oncology*,
T.L. Phillips and S. Leibel, Eds., W.B. Saunders Company,
Philadelphia, PA, 1994

Particle Radiation Therapy

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October 1994

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Prepared for the U.S. Department of Energy under Contract Number DE-AC03-76SF00098

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Textbook of Radiation Oncology

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Editors

Chapter 32A:

Particle Radiation Therapy

by

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This work was supported in part by USPHS NIH-NCI grant CA 19138 and by the DOE under contract No. DE-AC03-76SF00098.

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Introduction

The potential of particle beams for therapeutic application stems from, a) the precise dose localization possible with charged particles such as protons, helium or carbon ions because of the sharp dose fall off of the Bragg peak (**Figure 1**), and b) the biological attributes of high linear-energy transfer (LET) particles, including uncharged neutrons or heavy ions such as carbon, neon or silicon. The first clinical use of particle radiotherapy was in the pioneering *neutron* studies of Stone and Lawrence[1,2,3] starting in the late 1930's. *Charged particle* therapy was first proposed in 1946 by Wilson[4] and begun in the 1950's by Tobias and Lawrence[5]. However, fractionated charged-particle therapy of cancer was made practical only with the advent of computed tomography (CT) scanning to accurately determine the beam path in a patient. These studies have been carried out by Suit et al[6,7] at the Massachusetts General Hospital-Harvard Cyclotron Laboratory (MGH-HCL) since 1974 and Castro et al[8,9,10] at the University of California Lawrence Berkeley Laboratory and the Medical Center at San Francisco (UCSF-LBL) from 1975-1992.

At MGH-HCL, protons were available in limited energy and depth of penetration. This led to concentration of dose-localization studies on lesions primarily in the head and neck. At UCSF-LBL, ions ranging from protons through silicon became available in the 1970's with sufficient intensity and depth of penetration for clinical usage. At that time, intense interest was focused on the role of hypoxia in tumor therapy, and many observers expected significant biological gains from high-LET particles. Less attention was initially directed to the possible advantages of dose-localization although it was known that previous increases in the ability to deliver dose at depth had been accompanied by gains in local and regional control. Helium and neon ions were selected to be tested at UCSF-LBL, representing low-LET ions (helium) for their dose-distribution advantages and high-LET ions (neon) primarily for their biological advantages.

Basic Biological Characteristics of High-LET Charged-Particle Beams and Neutrons

Radiobiological studies have contributed to our understanding of the fundamental mechanisms of action of densely ionizing high-LET radiations at the molecular, cellular, tissue and organism levels. Although still not completely characterized, there is considerable experimental evidence that both qualitative and quantitative differences exist between the biological effects of photons and high-LET radiations. In addition, radiobiology techniques have been used to screen for differences in relative biological effectiveness (RBE) due to ion beam characteristics, modes of beam delivery, or dosimetric calibrations. Recent studies have also explored using radiobiological measurements to predict optimal patient selection for individual responsiveness of both tumor and surrounding normal tissues to radiations of different qualities[11,12].

Particle field characterization: Particle radiation fields become complex as the individual ions traverse absorbing material. *Linear energy transfer* (LET) is a physical parameter that is a measure of the mean rate of energy deposited locally along the track of a charged particle by electromagnetic interactions. LET is an important

quantity because the amount of radiation damage incurred by a cell depends on the number of ionizing events produced by the radiation presumably in the vicinity of the cell's DNA. Radiation damage along a particle track is caused by both direct mechanisms in which DNA molecules are ionized by the particle and indirect mechanisms in which free radicals, such as e^-aq, OH· and H·, produced by the ionizing particle react with the DNA. It is thought that changes in the genetic code, or changes in gene expression, of individual cells of the tumor and of the surrounding normal tissues, lead to local tumor control, and are also responsible for any undesirable normal tissue effects. One clear advantage of charged particles over photons is the control achievable in the mapping of the radiation fields to the tumor target.

LET values increase as charged particles slow down. The LET for 1-MeV electrons is 0.25 keV/μm. For neutrons produced in the reaction 50 MeV d + Be, the LET distribution ranges from 1.5 to 500 keV/μm with peaks near 8 keV/μm and 100 keV/μm[13]. Particles with LET less than 30-50 keV/μm are called low-LET particles, whereas those with larger LET values are categorized as high-LET particles **(Table 1).** High-LET particles are more biologically damaging primarily because there is evidence that they cause more severe, less repairable damage per unit track length than low-LET radiations[14,15].

Relative biological effectiveness (RBE): The concept of *relative biological effectiveness* arose from a variety of observations that have shown ionizing particulate radiations can be several times more effective per unit dose in producing biological effects than are x- or gamma-rays[16,17,18]. The International Commission on Radiological Units and Measurements defines RBE as the ratio of absorbed doses of two radiations required to produce the same biological effect[19,20]. One extension of this concept has been the use in the radiotherapy clinic of the terminology Gray-Equivalent (GyE) dose. This is the dose of a particle modality that yields an equivalent biological response to what is usually a higher dose of megavoltage xray or 60 Cobalt gamma-rays. The RBE for therapeutic neutron beams at a 2 GyE dose fraction ranges from 3.0 to 3.3 relative to 60 Cobalt. For 160-230 MeV proton beams the RBE is generally considered to be about 1.1, and for heavier particles (helium, carbon, neon, silicon) the RBE ranges from 1.2 to 4.5. The RBE depends on dose fraction size as well as the type of tissue irradiated and the position on the depth dose curve at which it is measured. Successful use of high-LET charged particle therapy requires understanding of the complicated dependency of RBE on these variables.

Oxygen Enhancement Ratio *(OER):* The *oxygen enhancement ratio* is the ratio of dose needed to inactivate well-oxygenated tumor cells relative to the dose needed for severely hypoxic or anoxic tumor cells. It has a value of about 3 for low-LET photons, electrons or protons, but is diminished with the use of high-LET irradiations to about 1.6 to 1.7 at LET values of about 100 keV/μm. The degree to which the OER is reduced is an indication of high-LET biological effectiveness.

Radiobiological Advantages of High-LET Radiotherapy

There are three major biological advantages to high-LET radiotherapy with neutrons or heavy ions: (I) hypoxic tumor cells are less radioresistant to high-LET radiations; II) there is less repair of radiation injury to cells; and (III) there is less variation of radioresistance through the cell-cycle phases.

I. Decreased radioresistance of hypoxic tumor cells to high-LET radiation

OER and RBE are functions of LET. While we now recognize that other factors than hypoxia are important in tumor control, most tumors have significant numbers of hypoxic cells which are preferentially killed with high-LET irradiations. However, the RBE for high-LET radiation is also increased for normal tissues as well as for tumors. Whether or not high-LET radiotherapy is effective in treating a given disease may depend more on the relative values of the tumor and normal-tissue RBEs than it does on reduction in the OER. As an example, the neon-ion RBE for late effects in CNS tissues is between 4 and 5.5 at a dose fraction of 2 GyE[21]. This implies that care must be taken in designing neon-ion treatments which involve irradiation of CNS structures by using multiple portals and exploiting the dose-localizing ability of these ions. Charged particles of high-LET have distinct dose-localizing advantages over neutrons which permit more selective deposition of biologically effective dose in the tumor relative to normal tissues.

II. Decreased repair of radiation injury

Decreased repair of radiation injury imparted by high-LET particles is evidenced by the absence of a shoulder on the cell-survival dose response curve for high-LET radiation, also implying that the RBE for high-LET particles is larger for smaller fraction sizes than it is for larger doses per fraction. Thus, it is important to recognize that using smaller doses per fraction of high-LET irradiation will not help spare normal tissues as is the case for low-LET radiation. In fact, Fowler[22] has recommended that large numbers of small dose fractions of neutrons should be avoided because such treatment schedules lead to unexpectedly severe late injury. Shortening the overall treatment schedule for high-LET radiation therapy to 2 to 3 weeks also minimizes the proliferation of tumor cells during treatment.

III. Less variation in radioresistance throughout the cell cycle

For several cell types tested *in vitro,* the late S phase has been shown to be most resistant to low-LET radiation[23]. In addition, Sinclair[24] reported that for HeLa cells there is a second phase of radioresistance in the relatively long G1 phase. This suggests that high-LET radiation might be advantageous treating either fast-growing tumors with a large proportion of cells in the S phase or treating slowly-proliferating tumors with a large fraction of cells in G1 or G0. An example is the use of high-LET radiation to treat slowly-growing soft tissue sarcoma, salivary gland tumors or prostatic tumors.

Variation in RBE Across the Spread-Bragg peak

Since the RBE depends on the LET of the particle, and since the LET of a charged-particle beam varies as a function of energy, and hence, depth of penetration,

the RBE for charged-particle beams varies across the spread-Bragg peak. The RBE is highest at the distal end of the peak where the LET is highest. Thus, to compensate for the variation in RBE across the spread-Bragg peak and to try to deliver a uniformly effective dose across the tumor volume, spread-Bragg peaks for heavy ion radiotherapy are sloped as illustrated in **Figure 1.** For the high-LET treatments undertaken at UCSF-LBL, the slope of these curves is determined by requiring that the biologic effect, as predicted by the linear-quadratic cell survival model (i.e., S = S0e-a D-b D2), be uniform across the spread-Bragg peak[25,26]. In the LBL work the variation in the linear-quadratic variables alpha and beta with LET is taken from the work of Chapman[27].

Physics And Treatment Planning Of Charged Particles And Neutrons

Basic Physical Properties of Charged-Particle Beams

Low-LET charged particles derive their therapeutic advantage from their physical properties. In the therapeutic energy range (for protons, between 70 and 250 MeV), charged particles lose energy primarily by ionizing and exciting electrons as they penetrate a medium. The energy deposited at a given depth is inversely proportional to the square of the particle's velocity. This leads to a sharp increase in dose, called the Bragg peak, at the maximum depth of penetration **(Figure 1)** with abrupt fall off of dose in a short distance.

The maximum depth of penetration (range) of a charged-particle beam is a function of the initial beam energy and can be adjusted by varying the energy or adding or removing absorbing material upstream from the patient. Variable thickness absorbers or compensators can be constructed to precisely control the beam penetration in three dimensions. The resulting isodose distributions **(Figures 2, 3)** can be made to conform closely to the target volume, allowing higher doses to be delivered to the target without exceeding the tolerance doses of surrounding healthy tissues. Multiple Coulomb scattering between charged particles and atomic nuclei changes the direction of motion of the incoming particles without significantly affecting their energy. The net result of a large number of these interactions is to increase the angular spread of the beam and, in complex heterogeneous regions, to degrade the sharpness of the Bragg peak[28,29,30,31]. The effects of multiple scattering increase as a function of decreasing particle mass. Electrons, for example, exhibit no Bragg peak due to multiple scattering. For protons and heavier charged particles, multiple scattering increases the penumbra width as a function of depth and increases the distance over which the Bragg peak falls from the maximum dose to a few percent of the maximum dose.

Heavy ions can also undergo inelastic nuclear interactions with atomic nuclei resulting in the fragmentation of either the incoming ion or the atomic nucleus. These fragments cause dose to be deposited beyond the Bragg peak in a fragmentation tail which must be considered in planning heavy-ion treatments.

Range Modulation

Although one of the first clinical applications of proton beams was to use the Bragg peak to treat small pituitary lesions[32], the unmodified Bragg peak is rarely used clinically because its width is far smaller than the width of most tumors. To treat large lesions, it is necessary to modulate the beam's range to spread out the Bragg peak, as shown in **Figure 1.** This is most commonly done with variable thickness absorbers such as the propeller or ridge filter shown in **Figures 4a and 4b.** The use of propellers was first proposed by Wilson[4,33], and working systems were later described by Koehler, Lyman and others[25,34]. As the blades of the propeller **(Figure 4a)** rotate through the beam, particles penetrating different thicknesses of plastic have their ranges correspondingly shortened. The resulting beam is the superposition of Bragg peaks with different ranges. Propellers are made of low-Z materials (e.g., Lucite) to minimize multiple scattering. By choosing the angular width of each blade appropriately, the spread-Bragg peak can be made uniform to within about 2%.

Ridge filters[26,35,36], such as the one shown in **Figure 4b** are made of heavy metals (e.g. brass) and consist of a series of closely spaced wedges. The mixing of particles with different ranges is accomplished through multiple scattering. These devices are used primarily for heavy charged particles (e.g. neon ions).

With passive beam-modulation techniques such as the propellers and ridge filters described above, the spread-Bragg peak width is constant over the entire tumor volume. Because most tumors have a variable thickness across the radiation field, some normal tissues immediately upstream from the target will receive the full dose delivered with that beam. An obvious way to minimize the dose just upstream from the target is to use several beam orientations in a given treatment plan. A more technologically challenging approach is to dynamically modulate the beam during the treatment using raster-scanning techniques to produce a beam with a variable spread-Bragg peak width across the radiation field. Chu et al[37,38,39] have described this raster-scanning technique and have developed a method for dynamic conformal therapy with charged particles which is ready to be introduced clinically. Dynamic charged particle conformal therapy has also been actively pursued at several other particle facilties including the Paul Scherrer Institute (PSI) in Switzerland (protons), Gesellschaft fur Schwerionen Forschung (GSI) in Germany (heavy ions) and the National Instititue for Radiological Studies (NIRS) in Japan (heavy ions).

Potential advantages of such a system have been evaluated[40,41,42,43]. Besides diminished dose to normal tissues, a reduction in the number of beam directions required to achieve a conformal plan is often possible **(Figure 5).**

Physical Properties of Neutron Beams

Fast neutrons undergo two basic types of interactions in tissue, elastic collisions and inelastic interactions. In elastic collisions, the incident neutron collides with a target nucleus, imparting energy to it in much the same way one billiard ball imparts energy to another. If the mass of the nucleus is comparable to the neutron mass, a large amount of energy is transferred. If, however, the nucleus is much more massive than the incoming neutron, the recoil nucleus travels only a small distance. For

example, the maximum range of a recoil hydrogen nucleus (consisting of a single proton) produced in an elastic collision with a 15-MeV neutron is approximately 2.5 mm, whereas, the maximum range of a heavy nucleus (e.g., carbon or oxygen) produced in the same collision is smaller by a factor of about 200. The LET of recoil heavy nuclei is, however, much greater than that of recoil protons (of the order of 800 keV/μm as compared to about 30 keV/μm[44].

Whereas in elastic collisions the target nuclei remains intact, in inelastic interactions, the target nuclei disintegrates producing fragment particles. This type of interaction results in the emission of alpha particles, protons, neutrons and gamma rays. However, most of the dose deposited in tissue by therapeutic neutron beams is a result of elastic rather than inelastic interactions. In particular, for 14-MeV neutrons, approximately 70% of the dose is deposited by recoil protons, less than 10% of the dose is a result of recoil heavy nuclei and as much as 30% is deposited by the products of nuclear disintegrations. Raju[44] has written an excellent review describing the physical properties of neutrons and issues related to neutron dosimetry. The interested reader is referred to this text for further details on this subject.

Treatment Planning for Neutron Beams

Depth-dose distributions for therapeutic neutron beams resemble photon depth-dose curves. The dose due to recoil protons builds up to a maximum beneath the skin surface in much the same way as electrons produce a build-up region in photon depth-dose curves. The skin-sparing effect for therapeutic neutron beams is greater for higher energy neutrons because recoil protons produced by these neutrons have higher energies and travel further in tissue. Higher energy neutron beams are preferred for radiotherapy because of their superior depth-dose distributions. The depth-dose curve for a 14-MeV neutron beam produced by a D-T generator resembles a 60 Cobalt depth-dose curve, whereas the depth-dose curve for a neutron beam generated by bombarding a beryllium target with high energy protons of 50 - 70 MeV is similar to that of a clinical 6 - 8 MeV photon beam **(Figure 6)**.

Treatment planning for neutron therapy is similar to photon treatment planning. Tissue heterogeneities do not perturb neutron dose distributions significantly and are usually not taken into account in treatment planning.

Treatment Planning for Charged-Particle Beams

To fully exploit the sharp distal edge of the Bragg peak, it is necessary to have an accurate 3-dimensional description of the tumor in relation to critical structures within the patient. This detailed anatomical information is provided by both CT and magnetic resonance imaging (MRI). Treatment planning for charged particles is inherently 3-dimensional, and many 3-dimensional treatment planning concepts were first introduced in the context of charged-particle therapy. The most important difference between treatment planning for charged particles and treatment planning for photons is that, in order to design tissue compensators that stop the beam at the distal surface of the tumor, it is essential to have a 3-dimensional tissue-density map for each patient. This detailed tissue-density information is provided by CT. Tissue

density data are inferred from the CT numbers[45] and used to design compensators which stop the beam at the distal surface of the tumor.

In charged-particle therapy, the treatment-planning CT scan takes the place of a treatment simulation in photon therapy. Because the CT data are used to design beam-modifying devices (i.e., compensators) which must be carefully registered with respect to the patient, the relation of the internal organs to each other must be the same during treatment as during the treatment-planning CT scan, insofar as this can be accomplished. This is most often achieved by immobilizing the patient in the treatment position. Immobilization techniques, as well as the subsequent steps in the treatment planning process, are described below.

Patient Immobilization and CT/MRI Scanning

After initial evaluation which includes a careful history and physical examination, precise daily positioning is obtained by use of an immobilization device which is individually constructed for each patient, generally from thermoplastic splinting material **(Figure 7a, 7b).** At the Loma Linda University Medical Center Proton Facility (LLUPAF), patients are immobilized supine in a specially constructed whole-body pod using a technique adapted from the pion therapy project at Paul Scherrer Institute (PSI) in Switzerland[46,47,48]. A planning CT scan and MRI are performed with the patient in the immobilization device and in treatment position when ever possible. MRI studies are increasingly important in outlining tumors and normal tissues, and are a vital part of the treatment planning process[49].

Target and Critical Structure Definition

Once the treatment-planning scans are obtained, the physician outlines the tumor and critical structures on all relevant slices of the CT scan. MRI images may also be used to identify the tumor volume. Volumes-of-interest defined on MRI must be transformed to CT because tissue densities derived from CT numbers are required for both dose calculations and compensator design[45]. This is accomplished using image-correlation techniques[50,51,52,53,54], based on matching external markers and/or matching anatomical structures or surfaces to determine the relative rotation, linear scaling and translation between the CT and MRI coordinate systems.

Beam Angle Selection and Collimator Design

Suitable beam entry angles are chosen, and customized beam collimators are designed by projecting the tumor volume and critical structure volumes in the "beam's-eye-view"[45,55,56] **(Figure 8)**. At present, experienced physicists and/or dosimetrists select possible beam angles with input from the physician, but future planning is likely to make use of "inverse" system algorithms which iteratively examine many angles to arrive at the best solution to the desired dose distribution (Brahme 91, Chu 93, Kallman 91)[57,58,59].

Tissue Compensator Design

After the beam orientations have been chosen and collimator margins defined, tissue compensators are designed for each treatment angle. These devices are usually fabricated from wax or Lucite **(Figure 9)** generally by computer driven milling machines, using output from the treatment planning code. To design a compensator, the water-equivalent distance along the beam trajectory to each point on the distal surface of the target volume is determined from the CT data. The *nominal* thickness of the compensator at each of these points is calculated by subtracting this water-equivalent distance from the beam range. The *actual* compensator thickness is then determined at each point by selecting the minimum thickness within some specified radius (usually between 0.1 and 0.3 cm) of that point. This operation is called "smearing" the compensator[60,61] and its purpose is to assure that the target receives the minimum prescribed dose even if the patient moves during treatment by an amount equal to the selected distance (i.e., between 0.1 and 0.3 cm).

Dose Calculations

An accurate assessment of the dose distribution on all CT planes through the tumor volume and surrounding critica structures is required for charged-particle therapy. At UCSF-LBL, charged-particle treatment planning and isodose calculations were performed using a computerized treatment planning system developed at LBL[45,62]. Similar programs have been developed at MGH-HCL, the Center for Protontherapie at Orsay, France (CPO), the National Institute of Radiological Science (NIRS), Japan and elsewhere. Three-D dose distributions **(Figures 2,3)** are most often calculated by computing the water-equivalent distance to each point using CT data and extracting the dose at these depths from a lookup table compiled from measurements made in a water-equivalent phantom. Three-D dose-volume histograms are a useful way to evaluate dose to target volumes and critical structures[63,64,65].

Currently utilized charged-particle dose calculations generally neglect multiple Coulomb scattering effects in complex heterogeneous regions, but are sufficient in most clinical applications. One way to adequately describe the effects of multiple-Coulomb scattering is to model the beam in terms of pencil-beam contributions[30]. Using this technique, the dose at a given point due to primary and scattered particles is determined by superimposing the contributions from pencil beams summed over the entire beam area. The more accurate pencil beam method is better at predicting inhomogeneities in dose within the target, the degradation in the distal fall-off in dose and the widening of the penumbra as a function of beam penetration due to multiple scattering.

For high-LET ions such as carbon, neon and silicon, which have differing biological effects from low-LET beams such as xrays, electrons or protons[66], the effects of high-LET must be accounted for in planning therapy, either by RBE corrections to create isodoses "equivalent" to low-LET irradiations or by using particle fluence to account for biological effects of individual particles. For helium and neon ions, at UCSF-LBL, the dose was tabulated in physical Gray and Gray-equivalent, although these concepts give a somewhat limited account of the biological effects[25]. Further study will be needed to see which is the best physical unit or biophysical

construct to use in planning the energy deposition from high-LET charged-particle radiation therapy.

Treatment Delivery and Verification

Positioning the patient for treatment and ascertaining that the patient remains in the same position throughout the treatment is critical for charged-particle radiotherapy[67]. This is most commonly done by comparing radiographic images taken with a back-pointing x-ray unit of the patient immobilized in the treatment position with digitally-reconstructed radiographs (DRRs). Projections of bony anatomy outlined on the CT scan may also be transferred to a transparent sheet and overlaid on the portal alignment film to verify the patient's position. Because of the accuracy required, the patient alignment process may require 10-30 minutes for charged-particle treatments and can be expedited by electronic portal imaging techniques.

Biological Dosimetry for Differing Modes of Beam Delivery

The type of charged-particle beam delivery system used can significantly affect the beam quality and consequent biological effects. The first systems used clinically broadened the pencil particle beams extracted from accelerators with a simple array of metal scattering foils to produce the field sizes required for treatment. As biological evidence indicated that the primary beam fragmentation processes occurring in the scattering foils contributed to a loss of beam quality and biological effectiveness, alternative methods of beam delivery were developed[37]. Particle atomic number and energy, as well as the techniques used to enlarge the beam field can change the effective LET value of the charged-particle beam. Biological systems such as human fibroblasts in culture are sensitive to the LET differences. Although the single-dose RBE data for clonal survival are not absolutely correct quantitatively for human tissue, they are proportional to human skin and mucosal RBE data for acute dose reactions. The relative changes in cell killing effects determined with *in vitro* techniques provide a quantitative basis for beam modulation design and input into the treatment planning model.

To make the fullest advantage of the dose localization capabilities of the charged-particle beams, one must use variable modulation over the field. Dynamic conformal therapy with the raster scanning system[37] allows the most effective "painting" of particle dose on the tumor while sparing the normal tissues **(Figures 5, 10 a, 10b)**. Biological dosimetry is needed to verify expected beam modeling and to confirm that scanned beams are properly shaped so as to be therapeutically useful.

Clinical Factors in Selection of High-LET Charged Particles

Heavy ions of atomic weight between carbon and silicon are of the most interest clinically[68]. The carbon ion beam has both biological and dose localization advantages superior to those of lighter ions such as protons. The ratio of dose in the tumor relative to the entrance region is maximized, and because carbon ions are heavier than protons, the beam penumbra is sharper. Carbon ion beams also have a smaller fragmentation tail than neon ions which can be dealt with more easily in treatment planning. Enough high-LET is present to provide significant differences in

DNA damage, and suppression of radiation repair. Double strand breaks are increased as is other evidence of DNA injury. These effects are maximized in the tumor by the use of the dose localization properties of charged particles.

Carbon, neon and silicon ions produce similar biologic effects. Biologically, these beams further reduce the OER and increase the RBE. Cells irradiated by neon and silicon ions show less variation in cell-cycle related radiosensitivity and decreased repair of radiation injury. However, the use of heavier ions such as neon and silicon leads to complexity in treatment planning because of the high-LET in the entrance region and the fragmentation tail. Normal tissues in these regions need to be carefully assessed and treatment plans designed which avoid significant late effects, especially in nervous system tissue.

Slowly growing tumors seem to be effectively treated by high-LET particles, both charged and neutrons. These include such histologies as salivary gland tumors, prostate gland tumors and some bone and soft tissue sarcoma. Additional studies are needed to understand the biological basis for this and to develop individual predictive assays to assist in selecting patients likely to benefit from these therapies.

Clinical Results With Protons And Helium Ions

Initial studies of proton therapy were begun in the 1950's at LBL by Tobias et al[5,69], and in Sweden at the University of Uppsala by Leksell, Larsson et al[70,71]. At LBL, the emphasis was on high doses and small fraction numbers for treatment of pituitary diseases, including pituitary tumors, diabetic retinopathy and suppression of pituitary function in metastatic breast cancer[72,73,74]. At Uppsala, functional neurological diseases were of initial interest with cancer therapy being done later until the accelerator was turned off in 1967. At MGH-HCL, protons became available for clinical work in the 1960's, leading initially to treatment of pituitary diseases and arteriovenous malformations (AVMs) by Kjellberg and associates[75,76,77,78], and later to cancer therapy by Suit and associates. Proton therapy also began in the 1960's at the Institute of Theoretical Physics in Moscow (ITEP) for pituitary diseases, in Japan at the National Institute for Radiological Science (NIRS) and later at the Proton Medical Research Center at Tsukuba (PARMS).

In 1974, Suit and associates[7,79,80,81,82,83,84,85,86] at MGH-HCL began long term studies of the dose-localizing properties of Bragg peak fractionated proton therapy in selected human tumors. Limitations of beam energy and depth of penetration at MGH-HCL relegated most clinical work to the head and neck, and other relatively superficial sites such as paraspinal and prostate gland tumors.

A clinical study was also begun at UCSF-LBL in 1975 by Castro and colleagues to determine the efficacy of heavy charged particles in the treatment of human cancers[8,10,87,88,89,90]. This study was predicated on the physical and biological advantages of heavy ions and aimed at defining whether dose localization and/or biological effectiveness would be most important clinically. The MGH-HCL and UCSF-LBL trials were the first extended studies of fractionated Bragg peak therapy in the treatment of cancer patients. This was made possible by the advent of CT scanning

and the development of sophisticated computerized 3D treatment planning. Over 17,000 patients have now been treated with charged particles, nearly 14,000 of these with protons. Proton facilities now exist in 10 countries with additional centers in several nations due to open soon.

Helium ions were used instead of protons at UCSF-LBL because they were technically easier to produce. However, they deposit a small amount of high-LET which must be accounted for in treatment planning, although insufficient to produce the clinical effects of heavy ions such as neon. The OER of helium ions has been measured around 2.5 - 3.0[11,68,91]. Their clinical effects are similar to protons, although they do exhibit RBE values of 1.2 - 1.4 for all tissues except CNS where a value of 1.6 was used. For comparison, the proton RBE used at MGH-HCL is 1.1[92]. The energies used were 150 - 232 MeV/amu for helium ions. Tumor doses were expressed in GyE by multiplying the charged-particle beam physical dose by the RBE representing the ratio of the photon beam dose to the charged-particle beam dose required for similar late effects.

The physical properties of heavy charged particles such as protons and helium ions are uniquely suited to precise localization of radiation dose **(Figure 2)** with limited irradiation of adjacent critical structures such as brain, cranial nerves and spinal cord[93,94]. For many tumor sites, their use permits delivery of equivalent tumor doses from 10-35% greater than can be delivered with standard xray therapy, with expectations of higher local control and survival rates.

The use of these ions in clinical practice required pretherapeutic and supportive efforts including biological studies, technical developments in CT and MRI tumor targeting, patient immobilization, beam delivery, patient dosimetry, and development of a 3D computerized treatment planning system. The experience at UCSF-LBL and MGH-HCL in the past 15 years has confirmed the usefulness of charged particles in increasing the tumor dose relative to normal tissue dose[86,95]. Significant increases in local control and survival have been demonstrated for a number of tumors as compared to historical data.

Irradiation of Skull Base Tumors With Charged Particles

The use of charged-particle radiation treatment in skull base tumors has progressively improved over the past 15 years with increasing precision of treatment planning and delivery. This has been associated with improved surgical techniques[96] for debulking difficult to reach tumors and carefully planned charged-particle irradiation based on improved diagnostic CT and MR imaging. As these tumors tend to remain localized, improved local control directly translates into improved survival. Among the factors of importance in irradiation of skull-based tumors are histology **(Table 2)**, tumor extent and whether treated for primary or recurrent disease.

At UCSF-LBL, from 1977 through 1992, 126 patients were irradiated with charged particles for tumors arising in the skull base[94,95,97]. One hundred nine patients were treated with helium ions. Seventeen of the 126 patients received a part of their therapy with neon ions and are included in the analysis.

Of the 126 patients, 53 had chordoma, 27 had chondrosarcoma and 27 had paraclival meningioma, with 19 patients having other histologies such as osteosarcoma or neurofibrosarcoma. The daily dose was 2.0 GyE, given in 4 fractions per week to total doses of 60 - 80 GyE (mean: 68 GyE). The RBE used for helium was ~1.3 for most tissues except for 1.6 for CNS. The limiting dose to brain stem was 60 GyE, for optic chiasm, 55 GyE and for cervical spinal cord, 45 GyE, using CNS RBE values of 1.6. Helium treatments at UCSF-LBL were often combined with photon treatment for 30-70% of the total dose due to limitations of beam availability. Local control and survival appeared improved compared to historical data in all tumor histologies. The Kaplan-Meier (K-M)[98] 5 year local control rates were 85% for meningioma, 78% for chondrosarcoma, 63% for chordoma and 58% for other sarcoma. For those patients treated with helium ions, the 5 year K-M local control rate for 23 patients with chondrosarcoma was 85%, and 70% in 48 patients with chordoma. K-M survival rates at 5 years were 82% for meningioma, 83% for chondrosarcoma and 72% for chordoma. As nearly as high a local control rate of 58% was seen in the other sarcoma histologies (including osteosarcoma) with a K-M survival rate at 5 years of 71%.

The K-M local control rates for the entire group of 126 patients with primary skull base tumors were 71% at 5 years and 57% at 10 years; K-M survival was 77% at 5 years and 62% at 10 years. For the 109 patients who were treated with helium ions, the 5 and 10 year K-M local control rates were 78% and 62%; the K-M survival rates for 5 and 10 years were 84% and 70%. The follow up ranged from 4 to 191 months with a median of 51 and a mean of 58 months.

The 5 year local control rate increased from 60% in the first patients treated (1977-1986) to 78% in the patients treated during the last 5 years, representing the influence of improved immobilization, treatment planning and delivery, and the availability of MRI for tumor delineation.

Since 1974, over 250 patients with skull base and cervical spine tumors, mainly chordoma and low grade chondrosarcoma, have been irradiated at MGH-HCL[6,82,85,99]. These studies have been most recently updated by Munzenrider et al[86] in a report of 194 patients irradiated for chordoma and low grade chondrosarcoma. The tumor doses ranged from 57-76 GyE, with a median of 68 GyE, using a proton RBE value of 1.1. Daily doses were usually 1.8 GyE given 5 days per week, usually 4 fractions of protons and 1 of megavoltage xray. Excellent results have been obtained with a local recurrence free survival of 76% at 5 years and overall survival of 90% at 5 years for the entire group. For chondrosarcoma, the local recurrence free survival was 95% at 5 years whereas with non chondroid chordoma, local recurrence free survival at 5 years dropped to 62%. The local recurrence free survival was diminished in women to 63% compared to 89% in males; this sex difference was seen only in non chondroid chordoma, not in chondrosarcoma. The reasons for the diminished results in women with skull base chordoma in the MGH-HCL series have not been elucidated, and this finding awaits further study and confirmation from other centers. Continued studies by the Proton Radiation Oncology Group (PROG) to optimize tumor doses are under way, especially for chordoma of the skull base where higher doses, up to 79 GyE, are being studied. Those patients with

tumors arising in the cervical spine did worse than those with skull base tumors with an overall survival at 5 years post treatment of 73% for the cervical spine versus 90% in the skull base.

Kaplan et al[100] evaluated the use of helium charged-particle radiotherapy in the treatment of residual or unresectable meningioma of the skull base or spine . Twenty-nine patients with meningioma were irradiated with helium ions at LBL during the period from 1981-1992, 26 for intracranial and 3 for spinal tumors. Total doses of 53-80 GyE with a mean of 63 GyE were delivered. The 10 year K-M local control and survival rates were 84% and 80% respectively. The only failures were in 4 patients treated early in the series with massive, recurrent tumors. Charged-particle radiotherapy is recommended for residual or unresectable meningioma adjacent to radiosensitive structures such as brain, cranial nerves or spinal cord.

At MGH-HCL, similar results have been obtained with proton therapy of paraclival meningioma. Austin-Seymour et al[82] reported on a group of 13 patients treated with proton therapy at MGH-HCL following subtotal resection. The median dose was 59.4 GyE, with a median follow up of 26 months. All 13 remained in local control.

It should be noted that 97 other patients treated at LBL for lesions arising from paranasal sinuses, nasopharynx or salivary gland, and extending into the skull base were also effectively treated with local control rates ranging from 45% to 83% depending on histology, and whether primary or recurrent disease[85,101]. Charged-particle treatment techniques and doses were similar in this group to those for primary skull base lesions.

Complications Of Charged-Particle Irradiation of the Skull Base:

The complication rate for the use of charged particles in the skull base has proven to be acceptably low, given the levels of dose required for control of these lesions. At MGH-HCL, Munzenrider[85,86,102] reported treatment-related morbidity including endocrine (28), auditory (36), visual (8) and brain (24) complications in 194 patients treated with protons for skull base chordoma and chondrosarcoma, for a complication rate of 34% (all grades) of all treated patients. However, grade 3-4 complications occurred in only 8% of patients. There were no grade 5 complications.

At UCSF-LBL, there were 85 of 126 patients with primary skull base tumors who had no evidence of disease from 1-15 years post therapy and could be evaluated for the presence of complications secondary to the charged-particle therapy[95,97]. During 1977-1986, when treatment planning relied on CT and treatment techniques were less well developed, 12 of 29 (41%) patients who had no evidence of disease had grade 3, 4 or 5 complications. From 1987-1992, MRI was utilized to delineate tumor volumes and image correlation techniques were developed to transfer data between MRI and CT. There were improved techniques for patient immobilization, tissue compensation and patient alignment and more information was available regarding normal tissue tolerance. In this era, the rate declined to 11 of 55 (20%) disease-free patients with grade 3, 4 or 5 complications. The complications observed were mainly cranial nerve injury including optic nerves, and radiation injury in the brain stem or temporal lobes.

Temporal lobe damage was manifested by MRI changes, memory deficits and varying severity of seizures. The major events in the patients at UCSF-LBL with severe complications were brain necrosis, osteoradionecrosis of the skull base, and severe temporal lobe injury. There were 4 out of 85 patients with Grade 5 complications, 3 in previously irradiated patients, 2 of whom received part of their treatment with neon ions.

With continued optimization of proton therapy for skull base tumors, we expect the serious complication level to be less than 5% for patients who have not been previously irradiated. The use of high-LET ions (heavier than protons or helium ions) is not advised, except with great caution, for skull base lesions, other than possibly for minor salivary gland tumors, because of the higher RBE for late damage to CNS structures.

Juxtaspinal and sacral tumors

Charged-particle therapy has been used at UCSF-LBL in the treatment of 62 patients with chordoma or chondrosarcoma of the spine and sacrum, with advantageous results[103,104]. Most patients received helium ions, often combined with photons, although some patients were treated with neon. The local control rates were lower than for skull base lesions: 50% (11 of 22 pts) for chondrosarcoma, with a follow up of 7-141 months, median of 31 months and 45% (18 of 40 pts) for chordoma, follow up of 6-167 months, median of 40 months. There was a trend for higher local control when neon ions were used with 6 of 8 chordoma patients controlled with neon ions versus 12 of 32 with helium ions.

For patients with juxtaspinal sarcoma (osteosarcoma, neurofibrosarcoma, malignant fibrous histiocytoma, etc) of the spine, local control was obtained in 16 of 29 patients. Follow up ranged from 4 to 128 months, with a median of 32 months.

Recently, Hug et al[105] updated the results in proton therapy of axial skeletal tumors at the MGH-HCL. Forty-seven patients treated between 1980 and 1992 were reviewed. The 5 year actuarial local control and survival rates were 53% and 50% for chordoma and 100% each for chondrosarcoma. For osteogenic sarcoma, a 5 year local control rate of 59% was obtained although overall survival fell to 44% in five years, mainly because of metastatic disease.

Lesions Adjacent to or Encircling The Brain Stem Or Spinal Cord

A specialized technique has been developed at UCSF-LBL for charged-particle irradiation of tumors partially or completely encircling the brain stem or spinal cord[106,107]. By dividing the target volume into two or more portions and using a combination of beams, a reasonably homogeneous irradiation of the target volume can be obtained which protects critical CNS structures from over irradiation **(Figure 11 a, 11 b)**. This technique requires knowledge of the physical and biological effects of the charged-particle beam to be utilized, reproducible patient immobilization to within +- 2 mm, careful treatment planning based upon Metrizamide contrast CT and/or MRI scanning, compensation for tissue inhomogeneities, and accurate, verifiable radiation delivery. Uncertainties in the dose distribution must be taken into account

when prescribing treatment. In the initial 47 patients treated using this technique[106] for a variety of tumors abutting the brain stem and spinal cord, including chordoma, chondrosarcoma, meningioma, osteosarcoma and metastatic tumors, the results showed a local control rate of 62%. Radiation injury to the spinal cord or brain stem, was low, occurring in only 3 patients, 2 of whom were being retreated after previous irradiation. This method has been continued to safely irradiate lesions encircling the brain stem or spinal cord to tumor doses of 60 GyE or more, generally higher than can be achieved with current low-LET irradiation techniques.

Uveal Melanoma:

Proton and helium ion irradiation of uveal melanoma has now been studied for more than 18 years with a remarkable consistency of results. Because of the ability to deliver a high local dose to a sharply confined target volume, there is an extremely high local control rate (~96%), high rate of retention of the eye (~85-94%), and preservation of useful vision in about 40-50% of patients. These treatments are now carried out in more than 10 countries around the world after being pioneered by Constable, Suit, Gragoudas et al at MGH-HCL[84,108,109,110,111] and Char, Castro et al at UCSF-LBL[87,88,112,113,114,115].

Excellent results have been reported[84,110,111,116,117] from MGH-HCL and the Massachusetts Eye and Ear Infirmary (MEEI) in an extensive trial of more than 1500 patients dating back to 1976. Proton therapy has been given in 5 sessions over 7-10 days to doses generally in the area of 70 GyE. A very high rate of local control (96%) has been achieved with preservation of the eye in 90% of patients. Visual acuity of 20/200 has been preserved in two-thirds of patients with uveal melanoma more than 3 mm from the fovea or optic nerve.

Munzenrider et al[110,111] reviewed the uveal melanoma patients from MGH-MEEI and found an enucleation rate of 10%, including tumor regrowth and complications of therapy. The leading risk factors for enucleation were ciliary body involvement, tumor height greater than 8 mm and proximity to the fovea. In a review[118] of MGH-MEEI proton treated uveal melanoma patients with metastatic disease, the liver was the most common site of spread. Metastases were detected from 7 weeks to 8 years post treatment with a median of 2.4 years. Only 13% of these patients survived 1 year after appearance of metastases. Gragoudas[84] reported on 1077 patients treated through 1987 with a very low rate of local recurrence (4%). Definitive evidence of recurrence was detected between 4 and 66 months post treatment, median: 19 months. Most failures were marginal recurrences or ring melanoma with only 3 clear in-field failures. Most patients with local recurrence were enucleated but some received conservative therapy. There was a trend to a higher rate of metastasis in patients with local recurrence.

At UCSF-LBL, 347 patients were treated from 1978-1992 **(Figure 7b)**. These patients were treated with various dose levels from 48-80 GyE given in 4-5 fractions over 4-16 days without a dose response being seen **(Table 3)**. A high local control rate of 96% has been seen at all dose levels and for large as well as small tumors. Of the 347 patients, 239 are still alive. The median follow up in all 347 patients is 72

months, range 3-176 months. Fourteen patients (4%) had local failure in the eye, requiring enucleation or re irradiation. Six of these 14 patients are dead of distant metastases. Forty-eight patients (14%) have required enucleation because of complications of the helium RT, mostly secondary to severe glaucoma refractory to medical or surgical therapy.

Of 308 patients who had 20/200 vision or better in the affected eye prior to treatment, 125 (41%) have retained at least 20/200 vision in the treated eye. However, large tumors (greater than 5 mm in ultrasound height) and those close to the optic nerve or fovea have a poor chance of retaining useful vision. Multivariate statistical analysis revealed that the strongest independent risk factors influencing vision outcome ($p < .05$) were tumor size, pretreatment visual acuity, tumor-fovea distance, and maximum tumor dose[115].

Since the relative efficacy of radioactive plaque therapy for uveal melanoma and charged-particle therapy is still not fully resolved, a total of 184 patients were entered into a comparison of helium ion therapy and 125 Iodine plaque brachytherapy in a randomized, dynamically balanced trial[88]. The tumors in eligible patients were less than 15 mm in maximum diameter and 10 mm in thickness. A minimum tumor dose of 70 GyE was delivered to the tumor apex with brachytherapy and 70 GyE in 5 fractions given with helium ion therapy. There was a significantly higher local recurrence rate after 125 Iodine brachytherapy than after helium ion irradiation. Enucleations occurred more frequently after brachytherapy. More anterior segment complications occurred after helium ion irradiation. Local control was significantly higher in the helium arm (100% vs 87%) and enucleations were lower (9% vs 17%). The conclusion of this trial was that charged-particle therapy is preferred for posterior lesions in the eye.

Currently nearly 20% of patients eventually manifest metastases which presumably were occult at time of therapy. At UCSF-LBL, 42 (16%) of 261 patients with ocular melanoma who were treated with helium ions between January 1978 and November 1986 developed metastatic disease and were reviewed by Nowakowski et al[119]. The time between start of helium ion treatment and recognition of metastatic disease ranged from 3 to 67 months (median 27 months). All 42 patients who developed metastatic disease died. The most common site of metastasis was the liver ($n = 34$). Multivariate analysis identified that anterior location of tumor ($p = .02$), and tumor diameter greater than 10 mm ($p = .0075$) predicted independently the development of metastases and lack of survival. Through 1992, 61 (18%) of the 347 helium patients developed distant metastases. Unfortunately, no effective adjuvant therapy has yet been reported.

A special case is melanoma involving the ciliary body which carries a poor prognosis when compared to all uveal melanoma. Decker et al[120] reported on 54 patients with ciliary body melanoma treated with helium ion irradiation between 1978 and 1985. Because of the high rate of metastatic disease, the 5 year disease specific survival rate was only 59% despite a 5 year local control rate of 98%. Multivariate analysis showed that the largest tumor diameter was the most important predictor of death from metastases. The incidence of neovascular glaucoma at 5 years was 43%. The 5 year actuarial rate of enucleation for pain and/or neovascular glaucoma was

26%. Analysis showed that treatment volume > 5.5 cc and initial ultrasound height > 9.2 mm to be predictive of development of neovascular glaucoma in 70% and 74% of patients respectively.

Proton therapy of uveal melanoma is now being successfully carried out worldwide in more than 10 countries, with large numbers of patients successfully treated at Paul Scherrer Institute-Switzerland (1448 pts), Centre de Protontherapie-Orsay, France (392 pts), Centre Antoine Lacassagne-Nice, France (328 pts), Douglas Cyclotron Unit-Clatterbridge, UK (513 pts) and others[121,122,123].

There are still further research questions to be studied in proton therapy of uveal melanoma including lowering the anterior chamber complications and finding effective therapy for those at risk for distant metastases. Further dose reduction and use of multiple ports as a means of diminishing the side effects in the anterior chamber of the eye are being studied using the Crocker Nuclear Laboratory cyclotron at UC Davis in conjunction with the Ocular Oncology Group at UCSF. At MGH-HCL-MEEI a randomized proton study comparing 70 GyE against 50 GyE is underway, also directed at attempts to preserve the high rate of local control and minimize complications. A continued search is needed for adjuvant therapy in patients with large and/or anterior tumors at high risk for metastatic disease.

Arterio-Venous Malformations

The dose localizing properties of protons and helium ions have been utilized for the stereotactic radiosurgical treatment of arteriovenous malformations (AVMs). Proton treatments of AVMs were begun by Kjellberg and associates at MGH-HCL where over 1300 patients have been treated[124]. More than 400 patients with surgically inaccessible intracranial vascular malformations have been treated with helium ions at LBL since 1980[125,126,127]. Over 250 patients with AVMs have been treated with protons at the Burdenko Neurosurgical Institute for Theoretical and Experimental Physics in Moscow and at the Leningrad Institute of Nuclear Physics by Minakova and Konnov and associates[128]. Other facilities performing these treatments include LLUPAF and the South African Proton Facility at Faure, South Africa.

Kjellberg[124] reported 20 year follow up on 709 patients in 1988, with partial or complete obliteration in most patients. With careful respect for volume of brain treated and dose, complications were acceptable. He concluded that proton beam radiosurgery was useful for inoperable or inaccessible AVMs.

In the LBL trial, doses up to 45 GyE were delivered to volumes ranging from 0.1 cm3 to 70 cm3. Fabrikant[125] reported that in the first 230 patients treated, the complete angiographic obliteration rate 3 years post treatment is between 90 and 95% for AVM treatment volumes less than 14 cm3, and between 60 and 70% for volumes larger than 14 cm3. The overall obliteration rate for all volumes (up to 70 cm3) is approximately 80-85%. No complications have occurred thus far in patients who received doses less than 25 GyE. However, for patients who received higher doses, the rate of serious complications, including symptomatic vasogenic edema (white

matter changes) and vasculopathy is 11%[125]. While highly effective in treating surgically inaccessible lesions, the disadvantages of charged-particle therapy for AVMs include the prolonged latency period before complete obliteration of the vascular lesion and the risk of serious neurologic complications.

Given the cost of the accelerator to produce protons, the role of protons versus linear accelerator or gamma knife radiosurgery is unclear. Protons may be of special value in some large, irregular lesions difficult to treat with xray techniques.

Clinical Experience with Neutrons and High-Let Charged Particles

Neutrons

Particle beams have been used to treat cancer since 1938 when Stone and Lawrence[2,3] first utilized fast neutrons to treat advanced malignancies at UCSF-LBL. At that time, the radiobiological differences between low- and high-LET radiation were not clearly appreciated, and surviving patients experienced significant late effects on normal tissues. Because of this, clinical use of particles went into hiatus in the 1940's and 1950's. In the 1950's and 60's, radiobiological studies better defined the characteristics of high-LET beams, and there was a reassessment of the Stone and Lawrence data[129]. Neutron clinical trials resumed in the United kingdom and Holland in the 1960's. Initially, encouraging results were obtained for some tumors which respond poorly to conventional treatment, especially in the head and neck[130,131].

Physics-lab based facilities in the US began phase I and II clinical trials with neutrons, pions, and heavy ions in the 1970's, and hospital- based neutron facilities became available in a few locations in the 1980's. As a result, phase I, II, and III clinical trials with neutrons have now been completed for a variety of malignancies.

The results of these studies have strongly suggested that neutron beams are superior for treating selected malignancies, particularly unresectable salivary gland cancers and unfavorable soft tissue sarcoma. Possible advantages have also been observed for locally advanced prostate cancer. On the other hand, results for primary tumors arising in the head and neck, brain, lung and pancreas have not been improved using neutrons.

Heavy Charged Particles

In 1979, a Phase I-II clinical trial was started at UCSF-LBL using high-LET charged particles (neon ions) to irradiate patients for tumors in which conventional treatment modalities were judged likely to be ineffective. Linstadt et al[90] initially reported on this trial in 1989 when a total of 239 patients had received a minimum neon physical dose of 10 Gy. By May 1992, when the Bevalac accelerator operation at LBL was terminated by the Department of Energy for budgetary reasons, a total of 299 patients had completed therapy receiving at least 10 Gy of neon ions.

Compared with historical results, the 5- year actuarial disease specific survival (DSS) and local control (LC) rates **(Table 4)** suggest that neon ion treatment

improves outcome for several types of tumors: advanced or recurrent macroscopic salivary gland carcinoma, paranasal sinus tumors, advanced soft tissue sarcoma, macroscopic sarcoma of bone, locally advanced prostate carcinoma and biliary tract carcinoma. The treatment of malignant glioma, pancreatic, gastric, esophageal, lung, and advanced or recurrent head and neck cancer was less successful although only limited numbers of patients were treated.

Salivary Gland Carcinoma

Worldwide, hundreds of patients treated on phase I-II studies with high LET beams for unresectable salivary gland cancer appeared to do better than conventionally irradiated historical controls. A phase III RTOG/MRC neutron trial for patients with unresectable salivary gland malignancies was reported in 1993[132]. Twelve patients were treated with conventional photon or electron irradiation, while 13 were treated with neutrons. The 10 year actuarial results showed a significant local control advantage for neutrons (56% vs 17%), although there was no overall survival difference. The majority of failures were distant for neutron patients, with locoregional recurrence the dominant failure pattern for conventional treatment. Severe side effects were more common in the neutron treated arm, but no fatal complications developed.

Linstadt[90] reported on 18 patients at LBL who were treated for unresectable primary or recurrent salivary gland malignancies with high-LET charged-particle beams of neon ions. The 5 year actuarial local control rate was 61% with a corresponding disease specific survival rate of 59%. Subsequent follow up in 1994[95] continued to show a significant local control and survival rate of about 60% at 5 years for minor and major salivary gland tumors treated with heavy charged particles.

The difference between photon and high-LET results have been sufficient to establish high-LET beams, either charged particles such as neon ions, or neutrons, as the treatment of choice for this type of malignancy.

Prostate Cancer

High-LET particle therapy may be beneficial for slowly growing tumors such as prostatic carcinoma. These beams offer the possibility of less radiation repair of high-LET injury as well as eliminating some variations in sensitivity during different phases of the cell cycle. In addition, areas of hypoxia within the tumor which are resistant to low-LET treatment are less so in the presence of high-LET irradiation. Heavy charged-particle conformal therapy also allows improved conformation of the high-dose zone to the target volume, namely the prostate, seminal vesicles and adjacent lymphatics.

Two phase-II Radiation Therapy Oncology Group/Neutron Therapy Clinical Working Group studies have now been completed comparing neutron vs proton treatment for locally advanced prostate cancer[133,134]. The first study[133], conducted from 1977-1983, analyzed 91 patients with either stage T3 N0 or N1 (stage "C" and "D-1") prostate cancers who were treated with either megavoltage irradiation (36 patients) or mixed photon/neutron beams (55 patients). Five year actuarial results showed a significant advantage to the neutron arm in terms locoregional failure (7% neutron vs 38% photon) as well as overall survival (60% vs 40%). However, there was no

difference in terms of developing distant metastases, with 36% of the neutron-treated patients and 44% of the photon-treated patients developing disseminated disease by the time of analysis. Ten year analysis continued to demonstrate an advantage for neutron-treated patients in terms of local control and overall survival[135].

A second trial using hospital-based neutron beams was implemented in 1986 for patients with stage T2, 3, 4; N0,1 ("B2", "C", "D1") disease[134]. Eighty-seven patients were treated with neutrons, and 85 with photons. Five year actuarial results were again significantly better for neutron patients in terms of locoregional failure (11% vs 32% for photons). There were no differences in terms of overall or disease-specific survival. Severe late complications were more common in the neutron treatment arm (11% vs 3%).

The interpretation of the neutron Phase III prostate trial results has been controversial, with some advocates claiming neutrons represent a significantly more effective form of treatment. Critics have challenged this view on the grounds of small study size, the high cost and limited availability of neutron therapy centers, and lack of any definite long term disease free survival advantage. In view of the relatively high neutron complication rates in the second trial[134], it has been suggested that had the photon arms employed doses sufficiently high to achieve equal toxicity, the local control and survival advantages might have disappeared. Also, it is unclear that neutrons would be superior to photons if compared to currently available high dose conformal photon techniques or combined androgen deprivation therapy + photon irradiation. Since the radiotherapeutic management of locally advanced prostate cancer continues to evolve, most oncologists consider high-LET neutron beams an encouraging modality, but not necessarily an established, superior form of treatment for prostate cancer.

Twenty-three patients have been treated at UCSF-LBL, with Stage B2 (8 pts) and C (15 pts) carcinoma of the prostate using neon ions for the cone-down "boost" portion of the therapy after pelvic irradiation with photons. Follow up ranges from 5 to 91 months with a median of 51 months. Four patients have died from prostate cancer, all from distant metastases. Four other patients have demonstrated metastases and are alive from 42 to 85 months post treatment. Two patients are scored as having local recurrence, although both are alive. In one patient a TURP biopsy was positive 5 months post completion of treatment, followed by orchiectomy now with no evidence of disease 4 years post therapy. The second patient had a positive biopsy in Australia, and is apparently free of disease on LH antagonists at 7.5 years post neon ion radiation treatment. A third patient has a recent elevation of PSA with a nodular prostate to palpation and may have local recurrence, although not yet confirmed by biopsy.

K-M local control is projected at the 84% level at 7.5 years post treatment in this small group of patients. K-M survival is 85% at 5 years post therapy and 64% at 7.5 years . High-LET charged-particle irradiation appears to diminish the local failure rate in locally advanced tumors to the level of 10-15%. However, 3 of the 23 patients have had rectal injuries, possibly attributable to the neon ion treatment. One patient had a very large tumor with the result that a larger than usual volume of rectum was treated. Anal sphincter stricture developed leading to colostomy. Another patient developed

an anterior rectal wall ulcer leading to a recto-vesical fistula requiring a colostomy and ileal conduit. A third patient had a colostomy following development of a rectal ulcer inferior to the neon target volume. These results indicate caution should be used in escalating doses in conformal therapy. For locally advanced prostate cancer, reduced volume irradiation with heavy ions such as neon after pelvic radiation therapy to 45-50 Gy should probably be in the range of 5-7 Gy (physical dose) or approximately 15-20 GyE.

Sarcoma

Conventionally treated patients with unfavorable soft tissue sarcoma have generally done badly, with long term local control rates only in the 38% range, compared to 80-90% for more favorably located lesions. Phase II trials involving 297 neutron-treated patients with unfavorable soft tissue sarcoma reported global local control rates on the order of 53%, suggesting a substantial improvement[136]. Similar improvement using neutrons has also been reported for osteogenic sarcoma and chondrosarcoma[131]. Since Phase III trials have not yet been completed comparing high-LET irradiation to photons for unfavorable soft tissue sarcoma, final conclusions regarding the role of high-LET beams for sarcoma cannot be made but initial results are promising.

Between 1978 and 1989, 32 patients with unfavorable soft tissue sarcoma underwent heavy charged-particle irradiation (helium and/or neon ions) with curative intent at Lawrence Berkeley Laboratory[89,137]. The tumors were located in the trunk in 22 patients and head and neck in 10. Macroscopic tumor was present in 22 patients at the time of irradiation. Two patients had tumors apparently induced by previous therapeutic irradiation. Follow up times for surviving patients ranged from 4-121 months (median 27 months). The 3-year K-M local control rate was 62%; the corresponding survival rate was 50%. The 3-year K-M control rate for patients irradiated with macroscopic tumors was 48%, while none of the patients with microscopic disease developed local recurrence (100%). The corresponding 3-year K-M survival rates were 40% (macroscopic) and 78% (microscopic). Patients with retroperitoneal sarcoma did notably well with the local control and survival rates 64% and 62%, respectively. Complications were acceptable and there were no radiation related deaths. Two patients (6%) required operations to correct significant radiation related injuries. These results appear promising and suggest that this technique merits further investigation, especially for retroperitoneal and pelvic lesions close to the G-I tract or CNS.

Bone Sarcoma

Between 1979 and 1989, 17 patients with unfavorable bone sarcoma who were treated wholly or in part with helium and/or neon ions at LBL were reviewed by Uhl et al[138]. The majority of tumors were located near critical structures such as the spinal cord or brain. Gross tumor was present in all but two patients at the time of irradiation. Six patients were treated for recurrent disease. Histologies included osteosarcoma, Ewing's sarcoma, and recurrent osteoblastoma. The follow up ranged from 7 to 118 months (median 40 months). The 5-year K-M local control rate was 48%; the corresponding survival rate was 41%. Over half the patients succumbed to distant

metastases despite the fact that the majority of patients received chemotherapy. From the results of this preliminary study, we believe that heavy charged-particle irradiation can be effectively used for control of locally advanced or unresectable bone sarcoma.

Head and Neck Cancer

Results with high-LET neutron beams for head and neck cancer have been less encouraging. Two Phase III RTOG trials have been completed which compared neutrons vs photons and mixed beam (neutron + photons) vs photons alone. The former trial showed an advantage for neutrons in terms of complete response (52% vs 17%), but there was no overall survival difference between the two groups[139]. The latter trial found no advantage to the high-LET arm in terms of control of the primary or overall survival[140]. Control of metastatic cervical lymph nodes was statistically superior for the mixed beam arm (complete response rated 69% vs 55%; 2-year adenopathy control rate 46% vs 33%), but this did not translate into a survival advantage[141].

Maor et al[142] reviewed the most recent international head and neck cancer fast neutron trial completed in 1991, and was a collaboration between several hospital-based cyclotrons in the US and UK. This trial compared 20.4 Gy of neutrons in 12 fractions over 4 weeks against 70 Gy of photons in 35 fractions over 7 weeks for treatment of locally advanced squamous carcinoma of the oral cavity, oropharynx and laryngopharynx. There was an increased complete response rate for neutrons but ultimate local and regional control rates were not significantly different, although there was a trend to a higher nodal control rate with neutrons (48% vs 39%, p=0.18). There was no significant survival difference between photons and neutrons. The neutron arm had a higher late complication rate. Their conclusion was that fast neutron therapy of advanced head and neck cancer could only be recommended where the short treatment schedule benefit might outweigh the risk of increased late effects.

Similarly, no advantage using neon ion irradiation was found in 13 advanced head and neck patients with squamous carcinoma treated in a Phase I-II trial at LBL[10,90].

Other Sites

A retrospective study by Schoenthaler et al[143] was performed analyzing patients with *bile duct adenocarcinoma* who received radiotherapy at UCSF-LBL between 1977 and 1987. Forty-eight patients were treated postoperatively with curative intent, 30 received photon therapy (median dose 54 Gy), and 18 were treated with helium and/or neon ions (median dose 60 GyE). Thirty-six patients in the study had gross residual disease; none had microscopically negative margins. The overall two year actuarial survival was 28%: 44% for particle treated patients and 18% for patients treated with photons (p = .048). The median survival was 23 months in particle patients and 12 months in photon patients. Local control was also improved, though less significantly, in patients treated with particles (median disease free survival 20 mos vs 4.5 mos, p = .054).

Subsequently, 10 additional patients were treated for a total of 28 patients receiving charged particles for biliary tract tumors. There are 7 survivors of these charged-particle patients, with follow up ranging from 5 to 100 months. However, many of these patients have had problems with late effects on bowel, secondary to the increased RBE for high-LET particles for the GI tract.

Pancreatic Cancer was examined in two randomized prospective studies. An RTOG study (49 patients) compared photons, mixed neutrons and photons, and neutrons alone. The median survival rates were 5.6 (neutrons), 7.8 months (mixed beam), and 8.3 months (photons). Differences were not significant[144]. An NCOG study (49 patients) compared helium ions with photons; concurrent 5-FU was given in both arms. Median survival was 7.8 months for helium and 6.5 months for photons (p=n.s.)[145,146]. Neon ions were used in 64 patients. The median survival was 7 months with one long term survivor (1.5% 5-year survival rate). This survival rate is similar to contemporary results using photons + chemotherapy. Similar findings were noted with *gastric cancer* and *esophageal cancer* using neon ions[90,147].

Malignant Glioma has also been examined extensively using high-LET beams. An RTOG dose-searching study using mixed photons and neutrons enrolled 190 evaluable patients. Median survival was 9.9 months for glioblastoma multiforme and 22 months for anaplastic astrocytoma; there was no difference between neutron doses[148]. These results were no better than those seen with conventionally treated patients. A poorer outcome was actually observed for anaplastic astrocytoma patients who received higher doses of neutrons, reflecting the extreme toxicity of high-LET radiation on normal brain tissue. Sixteen similar patients were treated at LBL with neon ions. There was only one long-term survivor (77 + months) in a patient with anaplastic astrocytoma[90,149]. A subsequent trial of high-dose neon ion therapy for glioblastoma did not show a significant benefit.

Non-small Cell Lung Cancer was evaluated using neutrons, photons, and mixed neutron/photon beams in a randomized RTOG study[150]. One hundred two patients were enrolled. There was no significant difference between arms in terms of overall response rate or survival. Three-year survival rates were 8% for photons, 16% for mixed beam, and 5% for neutrons. Fatal complications and radiation myelitis were observed only in neutron-treated patients. Treating 20 similar patients with neon ions yielded one long term survivor (5-year disease specific survival rate = 5%)[90].

Pion Therapy

Negative pi mesons represent a special case of charged particles which were tried clinically at the Los Alamos National Laboratory-University of New Mexico (UNM-LAMPF), Paul Scherrer Institute-Switzerland (PSI) and the University of Vancouver-Canada (TRIUMF) after first being proposed by Fowler and Perkins[151] and Kaplan, Schwettman and Bagshaw[152]. Pions are unstable charged particles with a mass intermediate between the electron and proton. In addition to the Bragg peak, negative pions also exhibit a unique phenomenon called stars that makes them particularly attractive for treating radioresistant tumors. As a negative pion slows down near the

end of its trajectory in tissue, it can be captured by one of the constituent atoms such as carbon, oxygen, or nitrogen, cascade down the atomic levels, and then be absorbed by the nucleus. The 140-MeV pion rest mass energy then appears as kinetic energy of the fragments produced when the nucleus disintegrates into a star of alpha particles, neutrons, and protons[13]. It was thought the combination of high-LET plus dose distribution would result in improved local and regional control of tumors.

Clinical trials were carried out at Los Alamos by Kligerman and Von Essen[46,153,154] and at PSI. However, in practice, pions exhibit neither the sharp physical parameters of protons or heavier ions, nor do they have as much deposition of high-LET as neon ions or neutrons. As a result, their realized potential has not been as great as initially hoped for, and they have largely been discontinued in clinical work, except at the TRIUMF facility in Vancouver, Canada, where randomized trials in glioblastoma and prostate cancer are just being completed (Pickles, personal communication 94).

At PSI, pions did exhibit promise in the treatment of unresectable soft tissue sarcoma where Greiner et al[48,155] reported an actuarial local control rate of 64% at 5 years in 35 patients with lesions in the retroperitoneum, pelvis, groin or thigh. The use of dynamic pion therapy, and further studies of dosimetry and dose fractionation, might have led to better therapeutic use of this modality[13].

Neutron Brachytherapy with Californium 252

Californium 252 is a man made radionuclide which emits a mixture of neutrons and gamma rays. With a half life of 2.64 years, it is practical for use in curietherapy, emitting a fission energy spectrum of neutrons with an average energy of 2.35 MeV and modal energy of about 1.5 MeV. ^{252}Cf decays by alpha particle emission and spontaneous fission. Beta particles result from the decay of the fission products as does gamma radiation in the range of 0.5 to 1.0 MeV. The metallic wall of the seeds stops the alpha particles and partially attenuates the beta and gamma dose rate to 1/3 the neutron dose rate at 0.5 cm distance from the source. Because of the increased relative biological effectiveness of the neutrons (RBE of about 6-7 at dose rates of 30-60 rads per hour), the greatest portion of the biologic effect is due to neutrons, for tissues close to the implant[156]. The OER is approximately 1.6 when compared to ^{226}Ra or ^{137}Cs at dose rates of 30 to 60 rads per hour. The OER for radium at these dose rates ranged from 2 to 2.5. At higher dose rates (over 100 rads/hour) such as might be obtained if high intensity ^{252}Cf is used in a specially shielded room for gynecologic therapy, the OER is about 1.9. At the University of Texas M.D. Anderson Hospital, an RBE of 5 for the combined neutron and gamma dose was utilized for ^{252}Cf interstitial implants[157,158].

The first clinical brachytherapy with ^{252}Cf was carried out by Castro and associates[158] at the M.D. Anderson Hospital in the late 1960's but subsequent studies have mainly been carried out by Maruyama et al[159] in the USA, in Russia[160], and in Japan. Some interesting results have been reported by Maruyama in the use of

^{252}Cf in irradiation of advanced tumors of the cervix uteri and endometrium[159,161,162]. He noted more rapid regression of tumors when ^{252}Cf implants were used prior to external irradiation, possibly because initial neutron therapy from ^{252}Cf have a greater effect on poorly vascularized, hypoxic tumors. More recently, he has reported promising results using a combination of chemoradiotherapy and ^{252}Cf in treatment of locally advanced carcinoma of the cervix uteri[163].

Although definitive utility of ^{252}Cf in clinical therapy has not been established, the use of ^{252}Cf in radioresistant tumors deserves further study. The timing and scheduling of neutron therapy is important and may lead to a significant advantage from ^{252}Cf in selected tumors. The possibility of using ^{252}Cf as a source of epithermal and thermal neutrons in Boron Neutron Capture Therapy of brain tumors has also been proposed by Maruyama and others[164].

Current Clinical Indications And Future Directions

Protons

The use of proton therapy in the treatment of unresectable or partially resectable neoplasms in critical locations such as the orbit, eye, skull base, juxtaspinal area, retroperitoneum or pelvis is clearly demonstrated to be of value. Ample clinical evidence is present in the initial studies to show the ability of protons to deliver higher tumor doses while preserving adjacent critical normal tissues. This has been associated with higher rates of local control and survival compared to previous results with megavoltage xray or electron beam therapy. However, in the future these results should be compared with those of dynamic conformal photon therapy, to determine the best application of these modalities for various tumor sites.

At other proton facilities around the world[122,123,165,166] clinical data confirming the usefulness of protons has emerged, notably from Tsujii and associates[167] at the Proton Medical Research Center, University of Tsukuba, Japan. As of September, 1990, 147 patients have been treated with curative intent. Eighty percent of patients received total doses of at least 70 Gy and more than half of the patients received 80 Gy or more. Fraction sizes ranged from 2.5 to 4 Gy per fraction. The best results were seen in head and neck, lung, esophagus, stomach, liver and uterine cancers. A particular area of success has been in irradiation of limited volume hepatocellular carcinoma. However, a small group of patients with GU tumors, especially prostate, bladder and kidney were also successfully treated for local control. The hallmark of the Tsukuba experience has been precise dose localization with minimal margins to spare normal tissues. Using these techniques, they have successfully delivered high local doses with excellent rates of local control, and point the way to further advances in proton therapy.

Proton therapy also needs to be tried in additional tumors now that improved hospital-based machines are coming into use. The availability of gantry proton beams, better tumor localization, 3D treatment planning, noncoplanar beams and other technological improvements should lead to improved utilization of protons in a

wider array of clinical sites. Protons may be of unique value in treatment of children where preservation of normal tissues is of paramount importance[168].

The cost of proton therapy must be judged against modern 3D conformal megavoltage techniques in a fair comparison. Proton accelerators have a higher initial cost but should be amortized over 30 years of useful life with several treatment rooms being served from a single accelerator. Room costs, treatment planning and immobilization costs will be the same for both techniques. When this type of cost analysis is done, protons appear very economically favorable to 3D conformal photon therapy.

High-LET Beams

Neutrons have demonstrated some advantages for certain types of tumors (salivary gland, prostate, sarcoma) but their clinical role remains undetermined, particularly in view of reported increased late effects.

High-LET charged particles such as carbon, neon or silicon ions have not had sufficient study to prove or disprove their merits in clinical therapy. Neon ions, while giving promising initial results, have had significant late effects on normal tissues. The use of carbon ions may obviate this problem while providing both dose localization and enough high-LET deposition for optimal results.

The locale for continuing these studies has shifted to Japan and Europe. The National Institute for Radiological Science (NIRS) in Chiba, Japan will begin clinical studies in 1994. An excellent accelerator at GSI, Darmstadt is slated to begin clinical work in 1996 in conjunction with the University of Heidelberg. There is not presently a US accelerator which can collaborate in these studies due to the unfortunate decision to prematurely close the LBL Bevatron. The cost of producing heavy ions is greater than for protons, so a demonstration of unique value for certain tumors would be required to justify such a machine. Potentially such value has been pointed to in the initial LBL trials but much work remains to be done. Future use of heavy ions would also be facilitated by developing smaller, cryogenic magnet machines which could be accommodated in less space or in a hospital setting.

Combining charged-particle therapy with sensitizing agents has been suggested in pretherapeutic studies[169] and deserves consideration for clinical trials. The use of charged particles allows precision delivery of high radiation doses to the tumor while minimizing the effects in normal tissues.

While much has been learned regarding the clinical potential of particles in radiotherapy, it is likely that a further generation of use will be needed to accumulate sufficient patients in rigorous clinical trials to fully assess their role in clinical practice. High-LET particle radiotherapy would certainly be aided by better modeling of LET effects but more radiobiological and dosimetric studies are required to achieve this goal. Some of the key questions are: How does one deal with dose in particle fields of mixed radiation quality? Which biological models are appropriate or necessary for estimating effectiveness of particle doses? How does one incorporate RBE values into

treatment planning? Is it necessary to measure tissue-specific RBE values? Are there combined effects of chemotherapeutic agents and particle radiations? How can the late normal tissue effects of high-LET radiations be minimized? What are the effects of dose-rate and altered fractionation regimens? Coupled with predictive assays to select patients with tumors likely to be helped by high-LET radiation, such data would put particle therapy on a more rational basis for the next century.

We are indebted to Jacquelyn J. Iler for research and editorial assistance in the preparation of this Chapter.

References

1. Lawrence JH, Nelson WO, Wilson H: Radiology 29:446, 1937

2. Stone RS: Neutron therapy and specific ionization. Am J Roentgen 59:771, 1940

3. Stone RS: Am J Roentgen, Rad Ther, Nucl Med 59:771, 1948

4. Wilson R: Radiological use of fast protons. Radiology 47:487, 1946

5. Tobias CA, Anger HO, Lawrence JH: Am J Roentgen, Rad Ther, Nucl Med 67:1, 1952

6. Suit HD, Goitein M, Munzenrider J, et al: Definitive radiation therapy for chordoma and chondrosarcoma of the base of the skull and cervical spine. J Neurosurg 56:377, 1982

7. Suit HD, Goitein M, Munzenrider JE, et al: Evaluation of the clinical applicability of proton beams in definitive fractionated radiation therapy. Int J Rad Onc Biol Phys 8:2199, 1982

8. Castro JR, Quivey JM, Lyman JT, et al: Current status of heavy charged particle radiotherapy at Lawrence Berkeley Laboratory. Cancer 46:633, 1980

9. Castro JR, Chen GTY, Blakely EA: Current considerations in heavy charged particle radiotherapy. Radiat Res 104(2):S263, 1985

10. Castro JR, Reimers MM: Charged particle radiotherapy of selected tumors in the head and neck. Int J Rad Onc Biol Phys 14(4):711, 1988

11. Blakely EA, Tobias CA, Ludewigt BA, et al: Some physical and biological properties of light ions. Proceedings Of PTCOG V And International Workshop On Biomedical Accelerators, 1986. LBL#22962, 1987

12. Peters LJ, Hopwood LE, Withers HR, et al: Predictive assays for tumor radiocurability. Cancer Treatment Symposia Vol 1, 1984

13. Petti PL, Lennox AJ: Hadronic radiotherapy. Ann Rev Nucl Part. Science, In Press, 1994

14. Barendsen GW: Responses of different linear energy transfer. In Ebert And Howard (eds): Current Topics Of Radiation Research, Vol 4. Amsterdam, North-Holland, 1968, pp 293-356

15. Belli M, Cherubini R, Ianzini F, et al: RBE-LET relationship for the survival of V79 cells irradiated with low energy protons. Int J Rad Onc Biol Phys 55:93, 1989

16. Zirkle RE: Biological effectiveness of alpha particles as a function of ion concentration produced in their paths. Am J Cancer 23:558, 1935

17. Zirkle RE: Biological effects of alpha particles In Duggar BM (ed): Biological Effects Of Radiation, Vol I, New York, McGraw-Hill, 1936,.pp 559-572

18. Zirkle RE, Tobias CA: Effects of ploidy and LET on radiobiological survival curves. Arch Biochem Biophys 47:282, 1953

19. ICRU (International Commission On Radiation Units And Measurements). Quantitative Concepts In Dosimetry And Radiobiology. Report 30, Washington DC, 1979, pp 49-52

20. ICRP (International Commission On Radiological Protection), RBE For Deterministic Effects. A Report Of A Task Group Of Committee 1 Of The International Commission On Radiological Protection. ICRP Publication 58, Oxford, Pergamon Press, 1990

21. Leith JT, Ainsworth E.J, Alpen EA: Heavy-ion radiobiology: Normal tissue studies. Adv Radiat Biol 10:192, 1983

22. Fowler JF: Rationales for high linear energy transfer radiotherapy. In Steel, G, Adams GE, Peckham, MJ (eds): The Biological Basis For Radiotherapy, New York, Elsevier, 1983, pp 261-268

23. Fowler JF: Nuclear particles in cancer treatment. Bristol: Adam Hilger, Ltd. 1981

24. Sinclair WK: Cell cycle dependence of the lethal radiation response in mammalian cells. Current Topics in Radiat Res Quart 7:264, 1972

25. Lyman JT: Heavy charged particle beam dosimetry. In: Advances in Dosimetry for Fast Neutrons and Heavy Charged Particles for Therapy Applications, International Atomic Energy Agency, 1984, pp 267

26. Petti PL, Lyman JT, Castro JR: Sensitivity of helium beam-modulator designs to uncertainties in biological data. Med Phys 18:506, 1991

27. Chapman JD, Blakely EA, Smith KC, et al: Radiobiological characterization of the inactivating events produced in mammalian cells by helium and heavy ions. Int J Rad Onc Biol Phys 3:97, 1977

28. Goitein M: A technique for calculating the influence of thin inhomogeneities on charged particle beams. Med Phys 5:258, 1978

29. Goitein M, Sisterson JM: The influence of thick inhomogeneities on charged particle beams. Rad Res 74:217, 1978

30. Petti PL: Differential-pencil-beam dose calculations for charged particles. Med Phys 19:137, 1992

31. Urie M, Goitein M, Holley WR, et al: Degradation of the bragg peak due to inhomogeneites. Phys Med Biol 31:1, 1986

32. Koehler AM: Use of protons for radiotherapy. Proceedings Of The Symposium On Pion And Proton Radiography, Fermi National Acelerator Laboratory, Batavia, IL, 1971, pp 63-68

33. Wilson RR: Phys Rev 71:385, 1947

34. Koehler AM, Schneider RJ, Sisterson JM: Range modulators for protons and heavy ions. Nucl Instrum Meth 131:437, 1975

35. Crowe K, Kanstein L, Lyman J: A large field medical beam at the 184-inch synchrocyclotron. LBL Report 4235, 1975

36. Petti, PL, Lyman JT, Renner TR, et al: Design of beam-modulating devices for charged-particle therapy. Med Phys 18:513, 1991

37. Chu WT, Ludewigt BA, Renner TR: Instrumentation for treatment of cancer using proton and light-ion beams. LBL Report-33403, UC-406,1993

38. Chu WT, Renner TR, Ludewigt BA: Dynamic beam delivery for three-dimensional conformal therapy. In Chauvel P, Wambersie A (eds): Proceedings of the EULIMA Workshop on the Potential Value of Light Ion Beam Therapy, Nice, France, EUR 12165 EN:295-328, 1988

39. Castro JR, Petti PL, Daftari IK, et al: Clinical gain from improved beam delivery systems. Radiat Envir Phys 31:233, 1992

40. Goitein M, Chen GT: Beam scanning for heavy charged particle radiotherapy. Med Phys 10(6):831, 1983

41. Urie M, Goitein M: Variable versus fixed modulation of proton beams for treatment in the cranium. Med Phys 16:593, 1989

42. Daftari IK, Petti PL, Collier JM, et al: Evaluation of fixed- versus variable-modulation treatment modes for charged-particle irradiation of the gastrointestinal tract. Med Phys 20(5):1387, 1993

43. Daftari IK, Castro JR: Comparative study of conformal treatment planning of prostate cancer: Photons versus protons. Submitted to Radiotherapy and Oncology, 1994

44. Raju M: Heavy Particle Radiotherapy, New York, Academic Press, 1980

45. Chen GTY, Singh RP, Castro JR, et al: Treatment planning for heavy ion radiotherapy. Int J Radiat Oncol Phys 5:1809, 1979

46. von Essen CF, Blattmann H, Bodendoerfer G, et al: Int J Rad Onc Biol Phys 11:217, 1985

47. Coray, A, Blattman, H, Pedroni, E: Patient preparation, treatment planning, and dose verification for dynamic radiotherapy with pions. In: Proceedings of 5th Annual Meeting of ESTRO, Baden-Baden, Germany, Sept. 8-10, Abstract, 1986, p 200

48. Greiner R, von Essen CF, Blattmann H, et al: Pion therapy at Swiss Institute for Nuclear Research (SIN). Int J Rad Onc Biol Phys 12(Suppl 1):98, 1986

49. Fraass BA, McShan DL, Diaz RF, et al: Integration of magnetic resonance imaging into radiation therapy treatment planning: Technical considerations. Int J Rad Onc Biol Phys 13:1897, 1987

50. Chen GTY, Kessler ML, Pitluck S: Structure transfer in three-dimensional medical imaging studies. Proceedings Of The National Computer Graphics Association, Dallas, 171, 1985

51. Kessler ML, Pitluck S, Petti PL, et al: Integration of multimodality imaging data for radiotherapy treatment planning. Int J Radiat Oncol Biol Phys 21:1653, 1991

52. Pelizzari C, Chen GTY: Accurate three-dimensional registration of CT, PET and/or MRI images of the brain. J Comp Aided Tomography 13:20, 1989

53. Petti PL, Kessler ML, Fleming T, et al: An automated image-registration technique based on multiple structure matching. Med Phys (Submitted) 1994

54. Phillips MH, Kessler ML, Chuang F, et al: Image correlation of MRI and CT in treatment planning of intracranial vascular malformations. Int J Rad Onc Biol Phys 20:881, 1991

55. Goitein M, Abrams M, Rowell D, et al: Multi-dimensional treatment planning. II. Beam's-eye-view back projection, and projection through CT sections. Int J Rad Onc Biol Phys 9:789, 1983

56. Zink SR, Lyman JT, Castro JR, et al: Treatment planning study for carcinoma of the esophagus: Helium ions versus photons. Int J Rad Onc Biol Phys 14(5):993, 1988

57. Brahme A, Kallman P, Lind B: Optimization of the probability of achieving complication free tumor control using a 3D pencil beam scanning technique for proton and heavy ions. In Itano A, Kanai T (eds): Proceedings of the NIRS International Workshop on Heavy Charged Particle Therapy and Related Subjects, Chiba, Japan, 1991, pp 124-141

58. Chu WT, Ludewigt BA, Renner TR: Rev Sci Instrum 64(8):2055, 1993

59. Kallman P, Lind BK, Brahme A: An algorithm for maximizing the probability of cmplication free tumor control in radiation therapy. Karolinska Institute, Stockholm University, preprint, 1991

60. Goitein M: Compensation for inhomogeneities in charged particle radiotherapy using computed tomography. Int J Rad Onc Biol Phys 4:499, 1978

61. Urie M, Goitein M, Wagner M: Compensating for heterogeneities in proton radiation therapy. Phys Med Biol 29:553, 1983

62. Singh RP, Castro JR, Pitluck S, et al: Past, present and future of the Lawrence Berkeley Laboratory treatment planning system. To be presented at XVII International Cancer Congress, Oct 30 - Nov 5, New Delhi, India, 1994

63. Lyman JT: Complication probability as assessed from dose volume histograms. Rad Res 104:S13, 1985

64. Lyman JT, Wolbarst AB: Optimization of radiation therapy III. A method of assessing complication from dose-volume histograms. Int J Rad Onc Biol Phys 13:103, 1987

65 Austin-Seymour M., Chen GT, Castro JR, et al: Dose volume histogram analysis of liver radiation tolerance. Int J Rad Onc Biol Phys 12:31, 1986

66. Kraft G, Kramer M, Scholz M: Let, track structure and models. Radiat Environ Biophys 31:161, 1992

67. Verhey L, Goitein M, McNulty P, et al: Precise positioning of patients for radiation therapy. Int J Rad Onc Biol Phys 22(2):289, 1992

68. Blakely EA, Ngo FQH, Curtis SB, et al: Heavy-ion radiobiology: Cellular studies. Adv Radiat Biol 11:195, 1984

69. Lawrence JH: Proton irradiation of the pituitary. Cancer 10:795, 1957

70. Larsson B, Leksell L, Rexed B, et al: The high-energy proton beam as a neurosurgical tool. Nature (London) 182:1222, 1958

71. Larsson B: Radiological properties of beams of high-energy protons. Rad Res (Suppl 7):304, 1967

72. Tobias CA, Lawrence JH, Born JL, et al: Pituitary irradiation with high energy proton beams. A preliminary report. Cancer Res 18:121, 1958

73. Lawrence JH, Tobias CA, Born JL: Acromegaly. Transactions of the American Clinical and Climatological Association 73:176, 1961

74. Linfoot JA: Heavy ion therapy: Alpha particle irradiation of pituitary tumors. In Linfoot JA (ed): Recent Advances in the Diagnosis and treatment of Pituitary Tumors, New York, Raven Press, 1979, pp 245-268

75. Kjellberg RN, Sweet WH, Preston WM, et al: Bragg peak of a proton beam in intracranial therapy of tumors. Am Neurol Assoc Trans 87:216, 1962

76. Kjellberg RN, Davis KR, Lyons SL, et al: Bragg-peak proton beam therapy for arteriovenous malformations of the brain. Clin Neurosurg 31:284, 1984

77. Kjellberg RN: Stereotactic Bragg peak proton beam radiosurgery for cerebral arteriovenous malformations. Ann Clin Res 18(Suppl 47):17, 1986

78. Kjellberg RN: Proton beam therapy for arteriovenous malformation of the brain. In Schmidek HH, Sweet WH (eds): Operative Neurological Techniques, Vol 1, New York, Grune & Stratton, 1988, pp 911-915

79. Suit H, Urie M: Proton beams in radiation therapy. J Nat'l Cancer Inst 84(3):155, 1992

80. Austin-Seymour M, Munzenrider JE, Goitein M, et al: Progress in low LET heavy particle therapy: Intracranial and paracranial tumors and uveal melanomas. Radiat Res 104:S219, 1985

81. Austin-Seymour M, Munzenrider J, Goitein M, et al: Fractionated proton radiation therapy of chordoma and low grade chondrosarcoma of the base of the skull. Neurosurgery 70:13, 1989

82. Austin-Seymour M, Munzenrider J, Linggood R, et al: Fractionated proton radiation therapy of cranial and intracranial tumors. Am J Clin Oncol 13(4):327, 1990

83. Austin-Seymour M, Urie M, Munzenrider J, et al: Considerations in fractionated proton radiation therapy: Clinical potential and results. Radiotherapy And Oncology 17(1):29, 1990

84. Gragoudas ES, Seddon JM, Egan K, et al: Long term results of proton beam irradiated uveal melanoma. Ophthalmology 94:349, 1987

85. Munzenrider JE, Liebsch NJ, Dubois W, et al: High dose fractionated combined proton and photon radiation therapy of chordoma and low-grade chondrosarcoma of the skull base and cervical spine: I. Results in adult patients. Int J Rad Onc Biol Phys 21(Suppl 1):166, 1991

86. Munzenrider JE, Liebsch NJ, Efird JT: Chordoma And Chondrosarcoma Of The Skull Base: Treatment With Fractionated Xray And Proton Radiotherapy. In Johnson JT, Didolkar MS (eds): Head And Neck Cancer, Volume III. Amsterdam, Elsevier Science Publishers, 1993

87. Char DH, Castro JR, Kroll S, et al: Five year follow-up of helium ion therapy for uveal melanoma. Arch Ophthalmol 108:209, 1990

88. Char DH, Quivey JM, Castro JR, et al: Helium ions vs I125 brachytherapy in the management of uveal melanoma: A prospective randomized dynamically balanced trial. J Ophthalmol 100(10):1547, 1993

89. Linstadt DE, Castro JR, Phillips TL, et al: Charged particle irradiation of soft tissue sarcomas (Abst). Ninth Annual Meeting of the European Society for Therapeutic Radiology and Oncology. Montecatini, Terme, Italy, Sept 12-15, 1990, p 284

90. Linstadt DE, Castro JR, Phillips TL: Neon ion radiotherapy: Results of the Phase I-II clinical trial. Int J Rad Onc Biol Phys 20:761, 1991

91. Blakely EA: Cell inactivation by heavy charged particles. Radiat Environ Biophys 31:181, 1992

92. Tepper JE, Verhey L, Goitein M, et al: In vivo determinations of RBE in a higher energy modulated proton beam using normal tissue reactions and fractionated dose schedules. Int J Rad Onc Biol Phys 2:1115, 1977

93. Saunders WM, Castro JR, Chen GTY, et al: Helium ion radiation therapy at the Lawrence Berkeley Laboratory: Recent results of a Northern California Oncology Group clinical trial. Rad Res 104(2):S227, 1985

94. Saunders WM, Chen GTY, Austin-Seymour M, et al: Precision high dose radiotherapy: Helium ion treatment of tumors adjacent to critical central nervous system structures. Int J Rad Onc Biol Phys 11:1339, 1985

95. Castro JR, Linstadt DE, Bahary JP, et al: Experience in charged particle irradiation of tumors of the skull base: 1977-1992. Int J Rad Onc Biol Phys 29 (4):647, 1994

96. Gutin PH, Crumley R, Castro JR: Treatment of cranial chordoma. Surgery for skull-base tumors. In Long DM (ed): Contemporary Issues In Neurological Surgery. Oxford, UK, Blackwell Scientific Publications, 1992, pp 254-264

97. Berson AM, Castro JR, Petti P, et al: Charged particle irradiation of chordoma and chondrosarcoma of the base of skull and cervical spine: The Lawrence Berkeley Laboratory experience. Int J Rad Onc Biol Phys 5(3):559, 1988

98. Kaplan EL, Meier P: Non parametric estimation from incomplete observations. J Am Stat Assoc 53:457, 1958

99. Austin JP, Urie M, Cardenosa G, et al: Probable causes of recurrence in patients with chordoma and chondrosarcoma of the base of skull and cervical spine. Int J Rad Onc Biol Phys 25(3):439, 1993

100. Kaplan ID, Castro JR, Phillips TL: Helium charged particle radiotherapy for meningioma: Experience at UCLBL. Int J Rad Onc Biol Phys 28:257, 1994

101. Feehan P, Castro JR, Phillips TL, et al: Recurrent locally advanced nasopharyngeal carcinoma treated with heavy charged particle irradiation. Int J Rad Onc Biol Phys 23(4):881, 1992

102 Urie M, Fullerton B, Tatsuzaki H, et al: A dose response analysis of injury to cranial nerves and/or nuclei following proton beam radiotherapy. Int J Rad Onc Biol Phys 23(1):27, 1992

103. Schoenthaler R, Castro JR, Petti PL, et al: Heavy charged particle irradiation of sacral chordoma. Int J Rad Onc Biol Phys. 26(2):291, 1993

104. Nowakowski V, Castro JR, Petti PL, et al: Charged particle radiotherapy of paraspinal tumors. Int J Rad Onc Biol Phys 22:295, 1991

105. Hug EB, Fitzek MM, Liebsch NJ, et al: Locally challenging osteo-and chondrogenic tumors of the axial skeleton: Results of combined proton and photon radiation therapy using 3-D treatment planning. Int J Rad Onc Biol Phys, In Press

106. Castro JR, Collier JM, Petti PL, et al: Charged particle radiotherapy for lesions encircling the brain stem or spinal cord. Int J Rad Onc Biol Phys 17(3):477, 1989

107. Daftari IK, Petti PL, Collier JM, et al: Effect of patient motion on dose uncertainty in charged particle irradiation for lesions encircling brain stem or spinal cord. Med Phys 18:1105, 1991

108. Constable IJ, Goitein M, Koehler AM, et al: Small field irradiation of monkey eyes with protons and photons. Rad Res, 65:304, 1976

109. Gragoudas ES, Goitein M, Koehler AM, et al: Proton irradiation of small choroidal malignant melanoma. Am J Ophth 83:665, 1977

110. Munzenrider JE, Gragoudas ES, Seddon J, et al: Conservative treatment of uveal melanoma: Probability of eye retention after proton treatment. Int J Rad Onc Biol Phys, 15:553, 1988

111. Munzenrider JE, Verhey L, Gragoudas ES, et al: Conservative treatment of uveal melanoma: Local recurrence after proton beam therapy. Int J Rad Onc Biol Phys, 17:493, 1989

112. Char DH, Castro JR, Quivey JM, et al: Helium ion charged particle therapy for choroidal melanoma. Ophthalmol 87:105, 1980

113. Char DH, Castro JR, Quivey JM, et al: Uveal melanoma radiation. Ophthalmol 96(12):1708, 1989

114. Linstadt D, Char DH, Castro JR, et al: Vision following helium ion radiotherapy of uveal melanoma: A Northern California Group study. Int J Rad Onc Biol Phys 15:347, 1988

115. Linstadt, DE, Castro JR, Decker M, et al: Long-term results of helium ion radiotherapy for uveal melanoma. Int J Rad Onc Biol Phys 19:613, 1990

116. Egan KM, Gragoudas ES, Seddon JM, et al: The risk of enucleation after proton beam irradiation of uveal melanoma. Ophthalmol 96(9):1377, 1989

117. Seddon JM, Gragoudas ES, Egan KM, et al: Uveal melanoma near the optic disk or fovea. Visual results after proton beam irradiation. Ophthalmol 94:354,1987

118. Gragoudas ES, Egan KM, Seddon JM, et al: Survival of patients with metastases from uveal melanoma. Ophthalm 98(3):383, 1991

119. Nowakowski V, Ivery G, Castro JR, et al: Metastases in uveal melanoma treated with helium ion irradiation. Radiology 178:277,1991

120. Decker M, Castro JR, Linstadt D, et al: Ciliary body melanoma treated with helium particle radiation. Int J. Rad Onc Biol Phys 19:243,1990

121. Egger E, Zografos L, Bohringer T, et al: Proton beam irradiation of uveal melanoma at PSI: Analysis of successes and failures. Abstracts of the XX PTCOG Meeting, Chester, England, 1994

122. Chauvel P, Brassart N, Herault J, et al: Status report of the proton and neutron facility in Nice. Abstracts of the XX PTCOG Meeting, Chester, England, 1994

123. Schlienger P, Desjardins L, d'Hermies F, et al: Preliminary results with one year minimum follow up of the first 146 uveal melanoma patients treated with protons at CPO (Orsay). Abstracts of the XX PTCOG Meeting, Chester, England, 1994

124. Kjellberg RN, Abe M: Stereotactic bragg peak proton beam therapy. In Lunsford LD (ed): Modern Stereotactic Neurosurgery, 1988, pp 463-470

125. Fabrikant JI, Levy RP, Steinberg GK, et al: Charged-particle radiosurgery for intracranial vascular malformations. Neurosurg Clin N Am 3(1):99, 1992

126. Levy R, Fabrikant J: Medical applications of stereotactic radiosurgery. In Phillips MH (ed): Physical Aspects of Stereotactic Radiosurgery, New York, Plenum Publishing, 1993, pp 239-278

127. Levy R, Fabrikant J, Frankel K, et al: Charged-particle radiosurgery of the brain. Neurosurg Clin N Am. 1(4):955, 1990

128. Raju MR: Proton radiobiology, radiosurgery and radiotherapy. Int J Radiat Biology, In press, 1994

129. Sheline GE, Phillips TL, Field SB, et al: Effects of fast neutrons on human skin. Am J Roentgen 3(1):31, 1971

130. Catterall M, Bewley DK, Sutherland I: Second report on a randomized clinical trial of fast neutrons compared with X- or gamma-rays in treatment of advanced head and neck cancers. Br Med J 1:1942, 1977

131. Griffin TW: Particle-beam radiation therapy. In Perez CA, Brady LW (eds): Principles and Practice of Radiation Oncology, 2nd ed. JH Lippincott, 1992, pp 368-387

132. Laramore GE, Krall JM, Griffin TW, et al: Neutron versus photon irradiation for unresectable salivary gland tumors: Final report of an RTOG/MRX randomized clinical trial. Int J Rad Onc Biol Phys 27:235, 1993

133. Laramore GE, Krall JM, Thomas FJ, et al: Fast neutron radiotherapy for locally advanced prostate cancer: Results of an RTOG randomized study. Int J Rad Onc Biol Phys 11:1621, 1985

134. Russell KJ, Caplan RJ, Laramore GE, et al: Photon versus fast neutron external beam radiotherapy in the treatment of locally advanced prostate cancer: Results of a randomized prospective trial. Int J Rad Onc Biol Phys 28:47, 1993

135. Laramore GE, Krall JM, Thomas FJ, et al: Fast neutron radiotherapy for locally advanced prostate cancer: Final report of an RTOG randomized clinical trial. Am J Clin Oncol 16:164, 1993

136. Laramore GE, Griffith JT, Boespflug M, et al: Fast neutron radiotherapy for sarcomas of soft tissue, bone, and cartilage. Am J Clin Oncol 12:320, 1989

137. Reimers M, Castro JR, Linstadt DE, et al: Heavy charged particle radiotherapy of bone and soft tissue sarcoma: A Phase I-II trial of the University of California Lawrence Berkeley Laboratory and The Northern California Oncology Group. Am J Clin Oncol (CCT) 9(6):488, 1986

138. Uhl V, Castro JR, Knopf K, et al: Preliminary results in heavy charged particle irradiation of bone sarcoma. Int J Rad Onc Biol Phys 24:755, 1992

139. Griffin TW, Davis R, Hendrickson FR, et al: Fast neutron radiation therapy for unresectable squamous cell carcinoma of the head and neck: The results of a randomized RTOG study. Int J Rad Onc Biol Phys 10:2217, 1984

140. Griffin TW, Davis R, Laramore GE, et al: Mixed beam radiation therapy for unresectable squamous cell carcinoma of the head and neck: The results of a randomized RTOG study. Int J Rad Onc Biol Phys 10:2211, 1984

141. Wells G, Koh W, Pelton J, et al: Fast neutron teletherapy in advanced epidermoid head and neck cancer. A review. Am J Clin Oncol 12:295, 1989

142. Maor MH, Errington RD, Caplan RJ, et al: Fast-neutron therapy in advanced head and neck cancer, a collaborative international randomized trial. Int J Rad Onc Biol Phys, in press

143. Schoenthaler R, Castro JR, Halberg FE, et al: Definitive postoperative irradiation of bile duct carcinoma with charged particles and/or photons. Int J Rad Onc Biol Phys 27:75, 1993

144. Thomas FJ, Krall J, Hendrickson F, et al: Evaluation of neutron irradiation of pancreatic cancer. Results of a randomized Radiation Therapy Oncology Group clinical trial. Am J Clin Oncol

145. Woodruff KH, Castro JR, Quivey JM, et al: Postmortem examination of 22 pancreatic carcinoma patients treated with helium ion irradiation. Cancer 53:420, 1984

146. Linstadt DE, Quivey JM, Castro JR, et al: Comparison of helium-ion radiation therapy and split-course megavoltage irradiation for unresectable adenocarcinoma of the pancreas. Radiology 168:261, 1988

147. Castro JR, Saunders WM, Chen GTY, et al: Helium charged particle radiotherapy of locally advanced carcinoma of the esophagus, stomach and biliary tract. Am J Clin Onc 6(6), 1983

148. Laramore GE, Diener-West M, Griffin TW, et al: Randomized neutron dose searching study for malignant glioma of the brain: Results of an RTOG study. Int J Rad Onc Biol Phys 14:1093, 1988

149. Castro JR, Saunders WM, Austin-Seymour MM, et al: Heavy charged particle irradiation of glioma of the brain. Int J Rad Onc Biol Phys 11:1795, 1985

150. Laramore GE, Baue M, Griffin TW, et al: Fast neutron and mixed beam radiotherapy for inoperable non-small cell carcinoma of the lung. Results of an RTOG randomized study. Am J Clin Oncol 9:233, 1986

151. Fowler PH, Perkins DH: The possibility of therapeutic applications of beams of negative pi-mesons. Nature 189:524, 1961

152. Kaplan HS, Schwettman HA, Fairbank WM, et al: A hospital-based superconducting accelerator for negative pi-meson beam radiotherapy. Radiology 108:159, 1973

153. Kligerman MM, West G, Decell JF, et al: Am J Roentgen 126:261, 1976

154. von Essen CF, Bagshaw MA, Bush SE, et al: Long-term results of pion therapy at Los Alamos. Int J Rad Onc Biol Phys 13(9):1389, 1987

155. Greiner R, Munkel G, Kann R., et al: Pion irradiation at Paul Scherrer Institute. Results of dynamic treatment of unresectable soft tissue sarcoma. Strahlentherapie und Onkologie 166(1):30, 1990

156. Hall EJ, Rossi H: The potential of Californium 252 in radiotherapy. Br J Radiol 48:777, 1975

157. Castro JR: Experimental brachytherapy: Californium 252. In Pierquin B, Wilson JF, Chassagne D (eds): Modern Brachytherapy, Chapter 33, Masson Publishing USA, Inc, 1987, pp 317-323

158. Castro JR, Oliver GD, Withers R, et al: Experience with Californium 252 in clinical radiotherapy. Am J Roentgen Rad Ther Nucl Med 117:182, 1973

159. Maruyama Y, Van Nagell JR, Yoneda J, et al: Clinical evaluation of ^{252}Cf neutron intracavitary therapy for primary endometrial adenocarcinoma. Cancer 71(12):3932, 1993

160. Vtyurin BM, Tsyb AF: Brachytherapy with Cf-252 in USSR: Head and neck, gynecologic, and other tumors. Nucl Sci Appl 2:521, 1986

161. Maruyama Y, Feola JM, Wierzbicki J: Study of biological effects of varying mixtures of Cf-252 and gamma radiation on the acute radiation syndromes: Relevance to clinical radiotherapy of radioresistant cancer. Int J Rad Onc Biol Phys 27:907, 1993

162. Maruyama Y, Mesina J, Yudelev M, et al: New understanding from Cf-252 brachytherapy trials and considerations for neutron therapy of bulky gyn carcinoma for future. Strahlenther Onkol 170(5):253, 1994

163. Maruyama Y, Bowen MG, Van Nagell JR, et al: A feasibility study of ^{252}Cf neutron brachytherapy, cisplatin + 5-FU chemo-adjuvant and accelerated hyperfractionated radiotherapy for advanced cervical cancer. Int J Rad Onc Biol Phys 29(3):529, 1994

164. Wierzbicki, J, Maruyama Y, Alexander CW: Cf-252 for teletherapy and thermalized Cf-252 neutrons for brachytherapy. Nucl Sci Appl A4:361, 1991

165. Slater JM, Archambeau J, Miller DW: The Proton Treatment Center at Loma Linda University Medical Center: Rationale for and description of its development. Int J Rad Onc Biol Phys 22:383, 1992

166. Tsunemoto H, Morita S, Ishikawa T, et al: Proton therapy in Japan. Rad Res (Suppl)104:S235, 1985

167. Tsujii H, Tsuji H, Inada T, et al: Clinical results of fractionated proton therapy. Int J. Rad Onc Biol Phys 25:49, 1992

168. Gademann G, Wannenmacher M: Charged particle therapy to pediatric tumors of the retroperitoneal region: A possible indication. Int J Rad Onc Biol Phys 22:375, 1992

169. Linstadt DE, Blakely EA, Phillips, TL, et al: Radiosensitization produced by iododeoxyuridine with high linear energy transfer heavy ion beams. Int J Rad Onc Biol Phys 15(3):703, 1988

Table 1

Particle	Charge	Mass	RBE
Electron	-1	1 m_e	1
Proton	1	1832 m_e	1.1*
Neutron	0	1835 m_e	3.0-3.3**
Pions	-1	276 m_e	1.0-1.8***
Helium ion	2	4 amu	1.25****
Neon ion	10	20 amu	2.5****

* Value used clinically at MGH-HCL.
** Values taken from Stewart et al, 1989.
*** Values taken from Raju, 1980.
**** Values are used clinically at UCSF-LBL. Helium RBE is for an 8 cm spread Bragg peak and a fraction size of 2.0 GyE. The neon value is also for an 8 cm Bragg peak but applies to a fraction size of 3.0 GyE.

Table 2

Results Of Skull Base Therapy With Charged Particles:

	UCSF-LBL	MGH-HCL*
5 Year Local Control:		
Meningioma:	85%	100%
Chondrosarcoma:	78%	95%
Chordoma:	63%	62%
Other Sarcoma:	58%	59%
5 Year Survival:		
Meningioma:	82%	100%
Chondrosarcoma:	83%	95%
Chordoma:	75%	81%
Other Sarcoma:	71%	44%

Follow Up: 4-191 mos, Median 51 mos, (UCSF-LBL)
2-211 mos, Median 40 mos, (MGH-HCL)

* (MGH data from refs. A-S 90, Munz 93)

Table 3

Comparative Dose Analysis of Helium Ion RT at
UCSF-LBL for Uveal Melanoma
(1978-1992)

Tumor Dose	# Pts	Local Failure	Enucleation (Comp)	VA >20/200	DM	Median Followup	mean US hgt (mm)
80 GyE	70	2 (3%)	10 (13%)	41%	26%	115 mos	6.3
70 GyE	156	5 (3%)	21 (13%)	41%	19%	67 mos	6.7
60 GyE	66	3 (5%)	10 (15%)	36%	9%	100 mos	7.2
48-50 GyE	55	4 (7.5%)	7 (13%)	45%	15%	41 mos	6.0
Totals	347	14 (4%)	48 (14%)	41%	18%	72 mos (3-176 mos)	6.6

Table 4

Results Of Phase I-II Trial of Neon Ion Therapy at UCSF-LBL:

Advanced or recurrent salivary gland carcinoma:	DSS 59%, LC 61%
Paranasal sinus tumors:	DSS 69%, LC 69%
Advanced soft tissue sarcoma:	DSS 56%, LC 56%
Macroscopic sarcoma of bone:	DSS 45%, LC 59%
Locally advanced prostate carcinoma:	KMS 90%, LC 91%
Biliary tract carcinoma:	DSS 28%, LC 44%

Berkson-Gage disease specific survival (DSS)
Kaplan-Meier survival (KMS)
Actuarial local control (LC)

Figure 1. Depth Dose Distribution for 215 MeV/amu Helium Ion Beam:

Example of unmodulated (monoenergetic) Bragg curve and modulated Bragg curve spread out as appropriate for clinical radiotherapy. In this case, a helium beam is illustrated although protons, carbon and neon beams are similar except for a larger fragmentation tail for heavier ions such as neon. The slope in the spread Bragg curve compensates for increasing LET by decreasing the physical dose acrosss the Bragg curve. A family of spread peaks from 1 to 15 cm is needed for clinical therapy of tumors of differing sizes.

Figure 2. Clival Chordoma Isodose Plan

A single slice from a helium ion isodose plan for treatment of clival chordoma. Multiple coplanar portals are utilized. Isodose lines are in RBE-corrected, equivalent dose to compensate for biological effects from the small amount of high-LET present in the helium beam. Dotted lines represent initial and cone down tumor volumes as determined from MRI and CT scans. A total of 72 GyE was given to the smaller target volume.

Figure 3. Heavy ion treatment plan

A representative heavy ion (carbon) treatment plan for biliary tract cancer consisting of 4 coplanar portals. The total dose was 60 GyE. Isodose lines represent biologically (RBE) corrected dose. 3-D dose volume histograms were utilized to assess the dose to liver and stomach as an aid in planning for this type of therapy.

Figures 4a, 4 b. Ridge Filters/Plastic Propellers to spread the Bragg peak

Insertion of some type of variable thickness absorber such as a 4a) Lucite propeller or 4b) brass ridge filter has the effect of modulating or spreading the Bragg peak from a narrow width to a clinically useful width which will cover the desired target volume (see spread Bragg peak as shown in Figure 1). Particles penetrating different portions of the propeller or ridge filter have different ranges in tissue depending on the thickness of material they traverse.

Figure 5. Fixed and variable modulation dynamic charged-particle conformal therapy

Static charged particle therapy is shown in upper panel with stopping of the beam along the distal edge of the target volume. Lower panel shows a schematic representation of the LBL technique utilizing a dynamic collimator and variable energy absorber to irradiate in a stepwise fashion. The most distal layer in the target volume is irradiated first. The range of the beam is then shortened and the field shape is adjusted with the dynamic multileaf collimator to irradiate subsequent layers. This technique gives added sparing of normal tissues proximal to the target volume as well as stopping the beam along the distal edge of the target volume, and should lead to an even higher therapeutic ratio than current techniques (Courtesy of Chu et al. 88,93).

Figure 6. Neutron dose comparision

Example of neutron isodose plan for single beam compared to 6 Mv photon beam shows that neutrons produced from high energy cyclotrons are quite comparable to 6 Mv photons in clinical use.

Figures 7 a, 7 b. Immbolization devices for charged particle therapy

An example (a) of a typical patient set up for head/neck treatment at UCSF/LBL. A thermoplastic individually constructed head mask is made. Figure b shows a set-up of a patient in a perspex mask for treatment of uveal melanoma. This patient was treated in a lateral decubitus position, although seated positioning is more commonly used.

Figure 8. Beams-eye view of portal

The inner outline on this beams-eye projection is the projected tumor volume, and the outer outline represents the beam collimator which is obtained by adding an appropriate margin around the projected tumor volume to assure that this volume receives no less than 90% of the prescribed dose. The margin must be sufficient to assure that the patient receives this dose even if he moves during the treatment by 0.2 to 0.3 cm. For head and neck treatments, collimator margins of 0.3 cm are commonly used. For treatments in the thorax and pelvis, collimator margins are generally larger, between 0.5 and 1.0 cm.

Figure 9. Compensator

A tussue compensator is designed from the treatment planning program based on CT derived tissue density data. These compensators are generally milled from plastic or lucite using a computer code to drive the milling or drilling machine. Each charged particle portal requires an appropriate tissue compensator. Individual patient beam shaping collimators and tissue compensators are designed and fabricated from the 3-D LBL computerized treatment planning system.

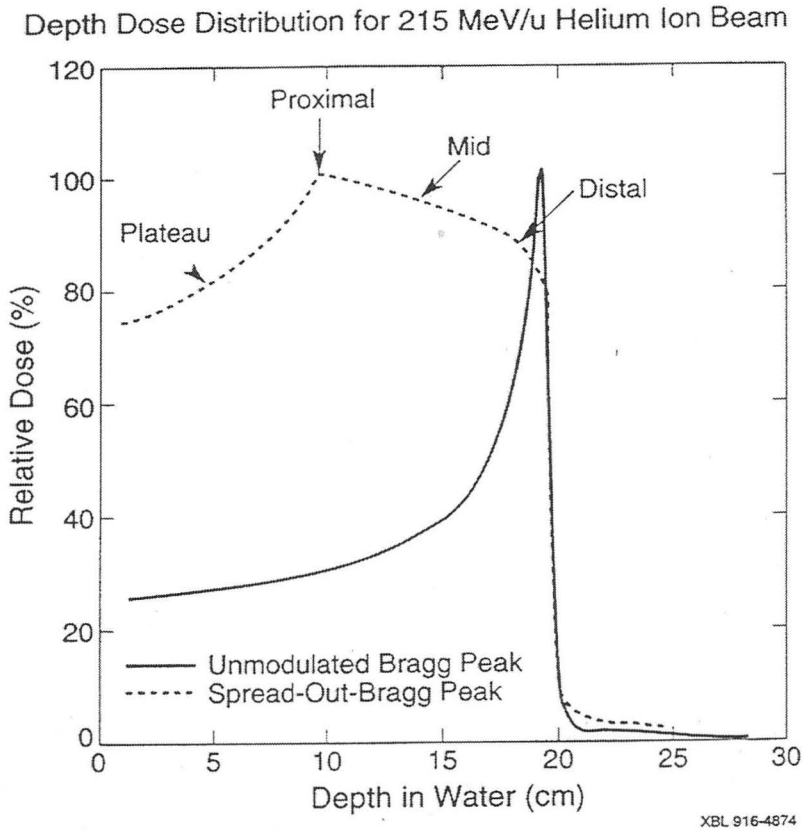
Figures 10a, 10b. Prostate treatment plans

Comparision of (a) 6-field coplanar 18 Mv xray conformal plan for irradiation of the prostate with (b) a computer simulation of a plan using dynamic conformal proton therapy. Better conformation of the high dose zone to the target volume is observed with the conformal proton therapy. Evaluation of several target sites for proton and heavy ion therapy have suggested clinical gains when moving from static charged particle therapy to dynamic conformal charged particle therapy (Courtesy of I. Daftari, Ph. D.).

Figures 11a, 11b. Divided target technique for irradiation of para-CNS tumors

Example of use of charged particles to irradiate a target volume wrapped around a critical structure such as the spinal cord (a). A large chondorsarcoma was present abutting and encircling the spinal cord and cauda equina and invading into the vertebrae (b). After subtotal resection a combined photon and charged particle plan was devised to irradiate the target volume and minimize dose to the CNS. The target volume indicated by the heavy dotted line received a total of 70.6 GyE except for the inner region around the spinal cord which received less than 46 GyE. Computerized 3-D treatment planning based on Metrizamide CT scanning, together with precise immobilization and treatment delivery, is needed to accomplish this technique without CNS injury.

Fig. 1


Depth Dose Distribution for 215 MeV/u Helium Ion Beam
Proximal
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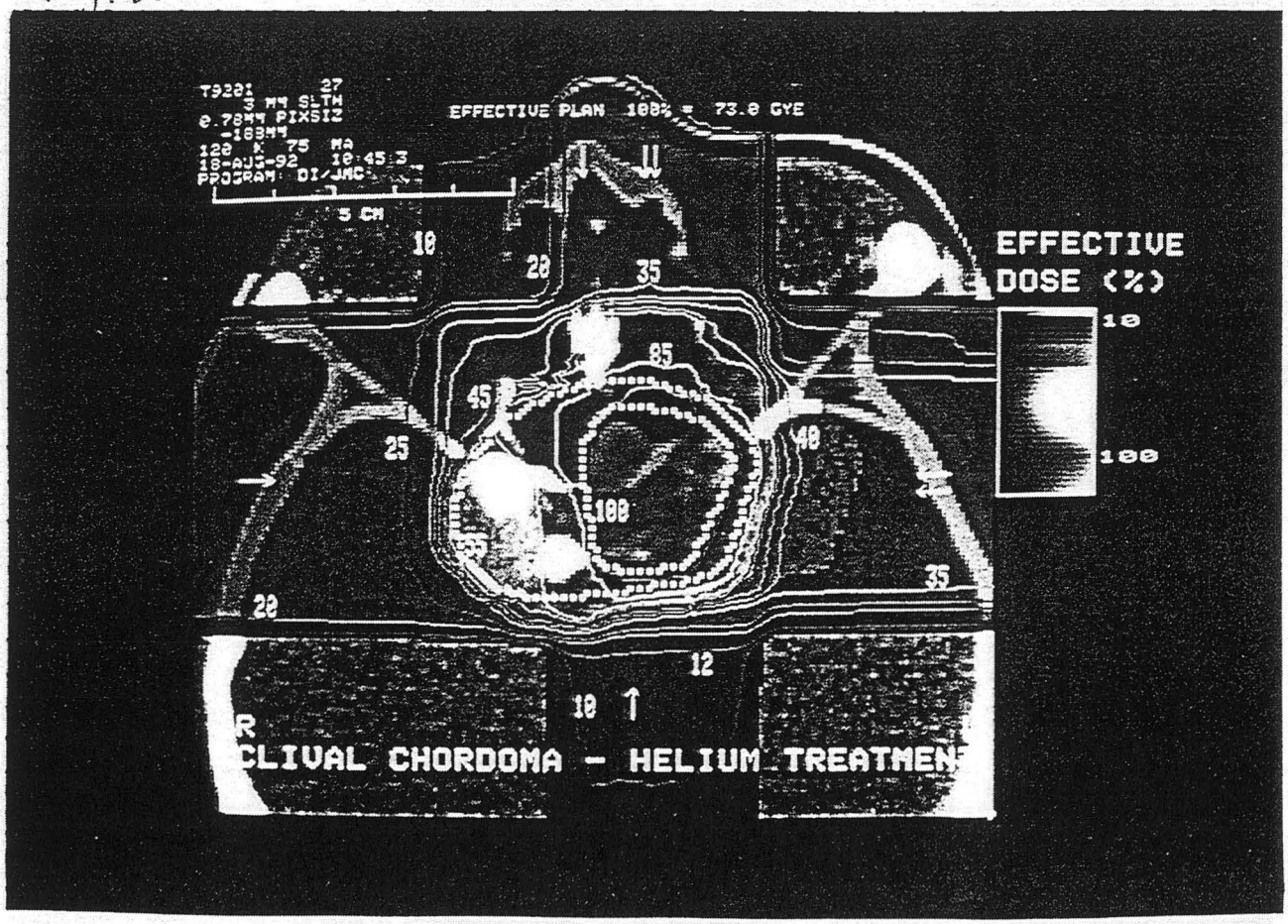
Distal
Plateau
Relative Dose (%)
Depth in Water (cm)
Unmodulated Bragg Peak
Spread-Out-Bragg Peak
XBL 916-4874

Fig. 2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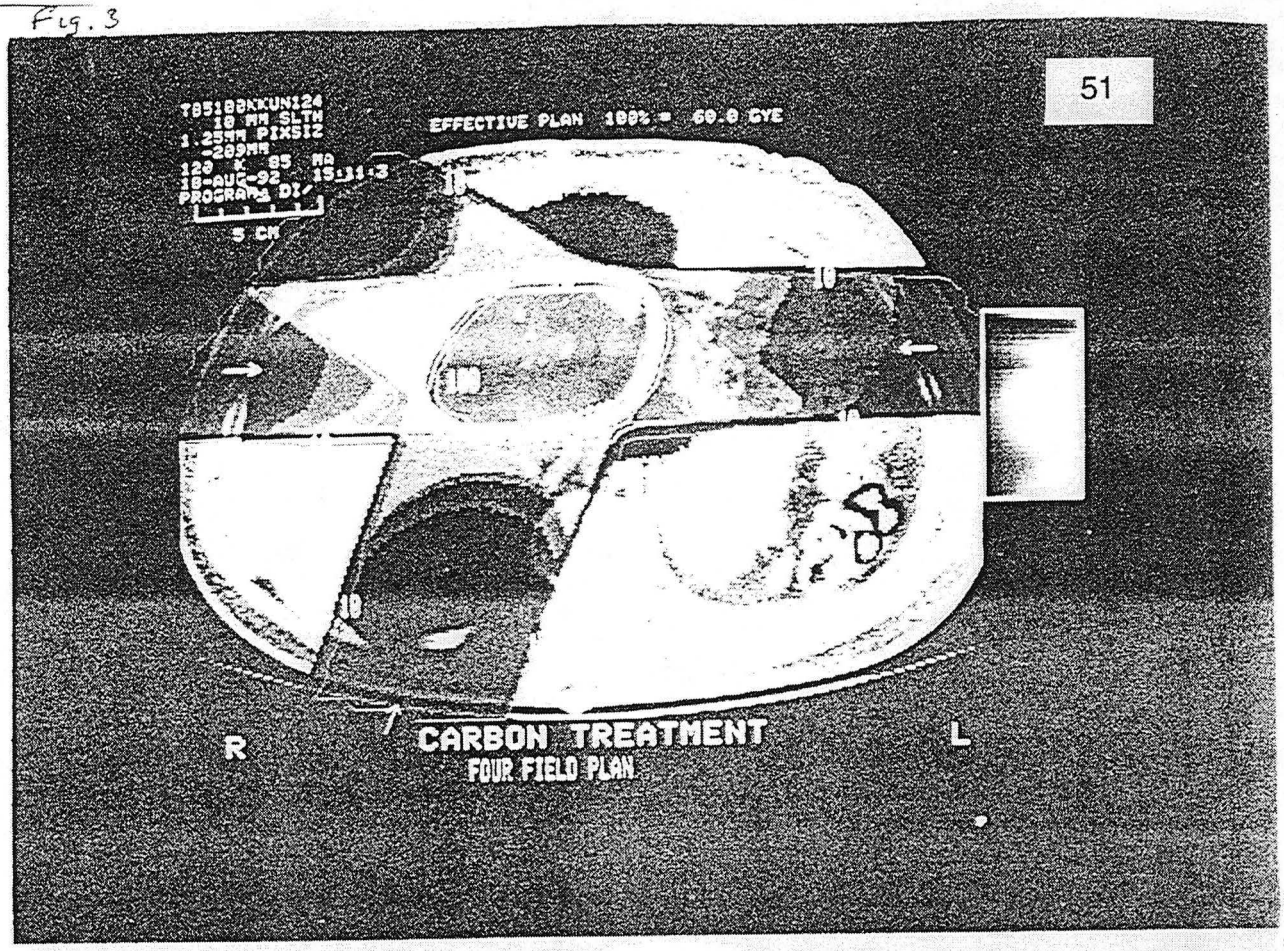
EFFECTIVE
DOSE (%)
10
100
CLIVAL CHORDOMA - HELIUM TREATMEN

Fig. 3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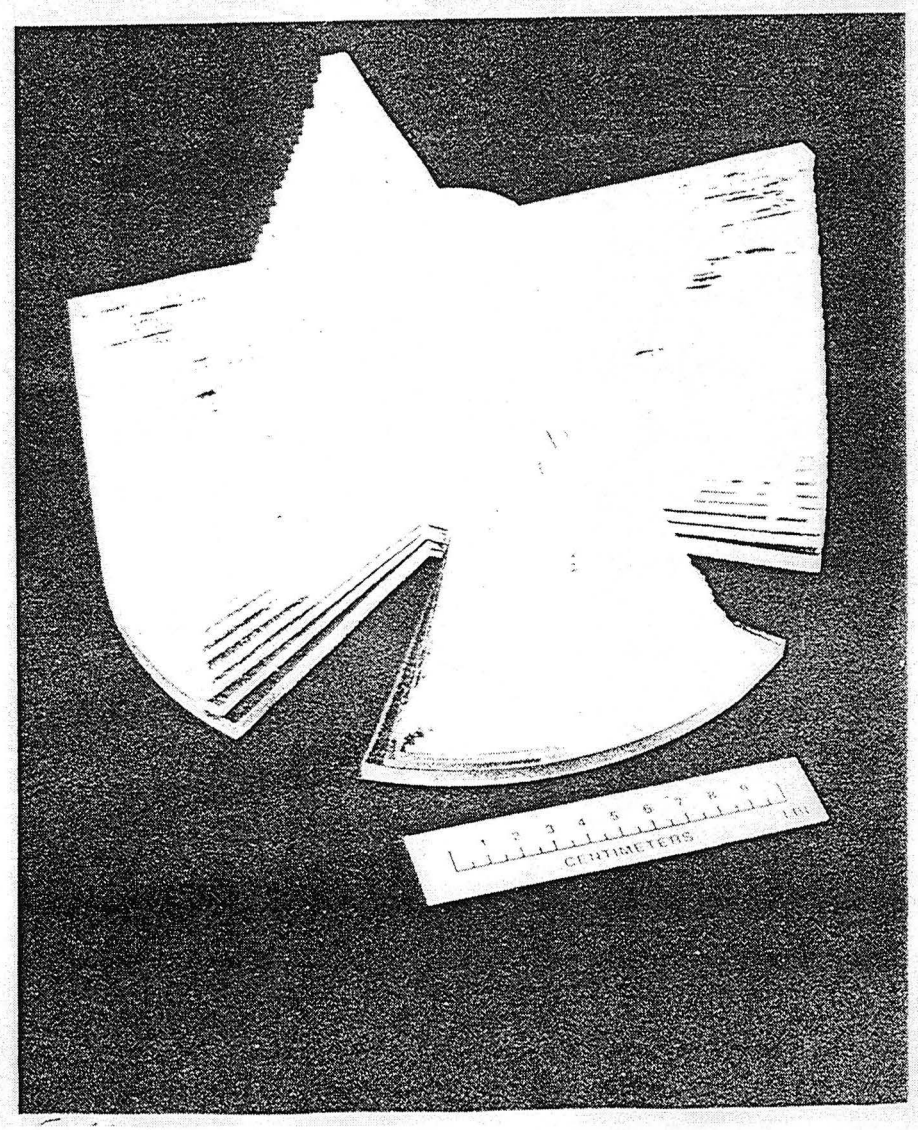
R
L
CARBON TREATMENT
FOUR FIELD PLAN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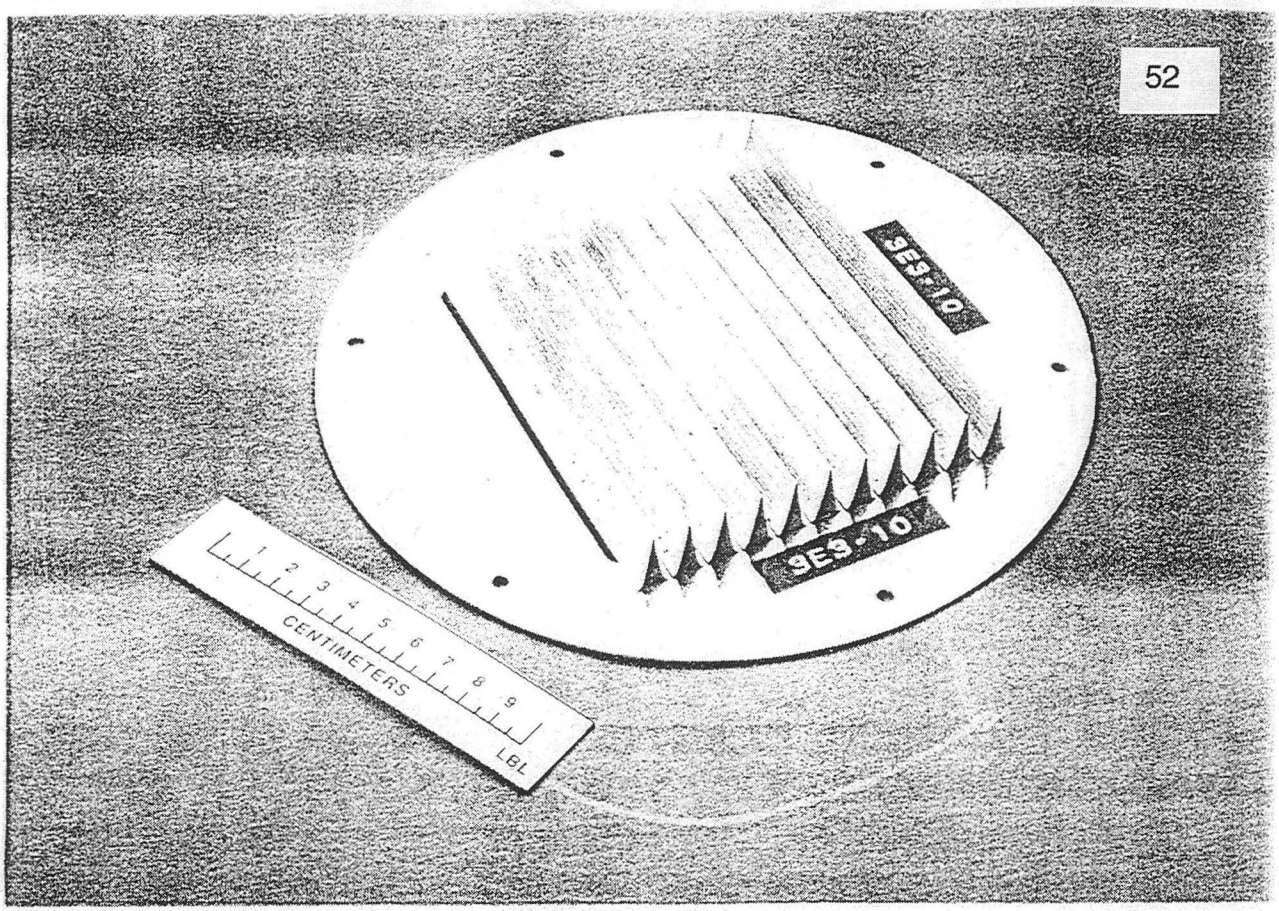
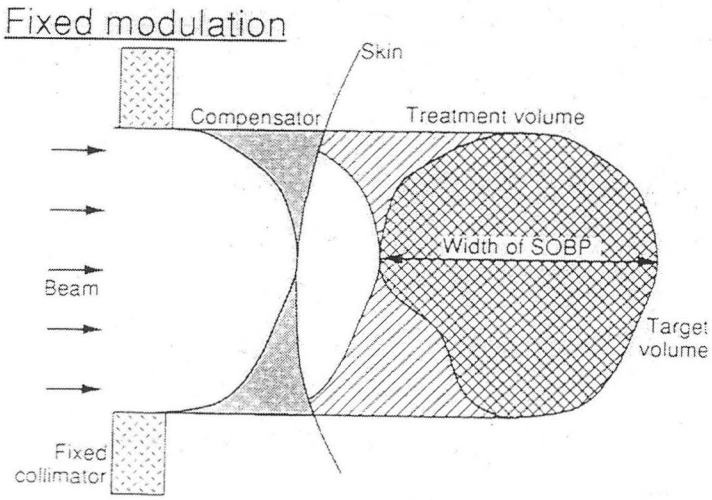
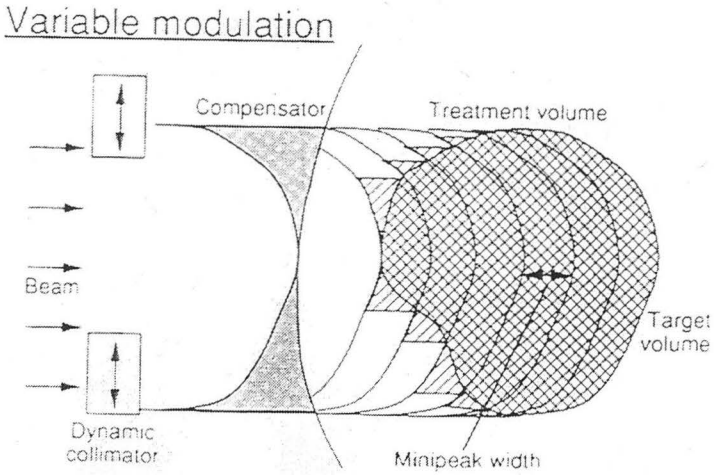


Fig. 4b





XBL 919-1958

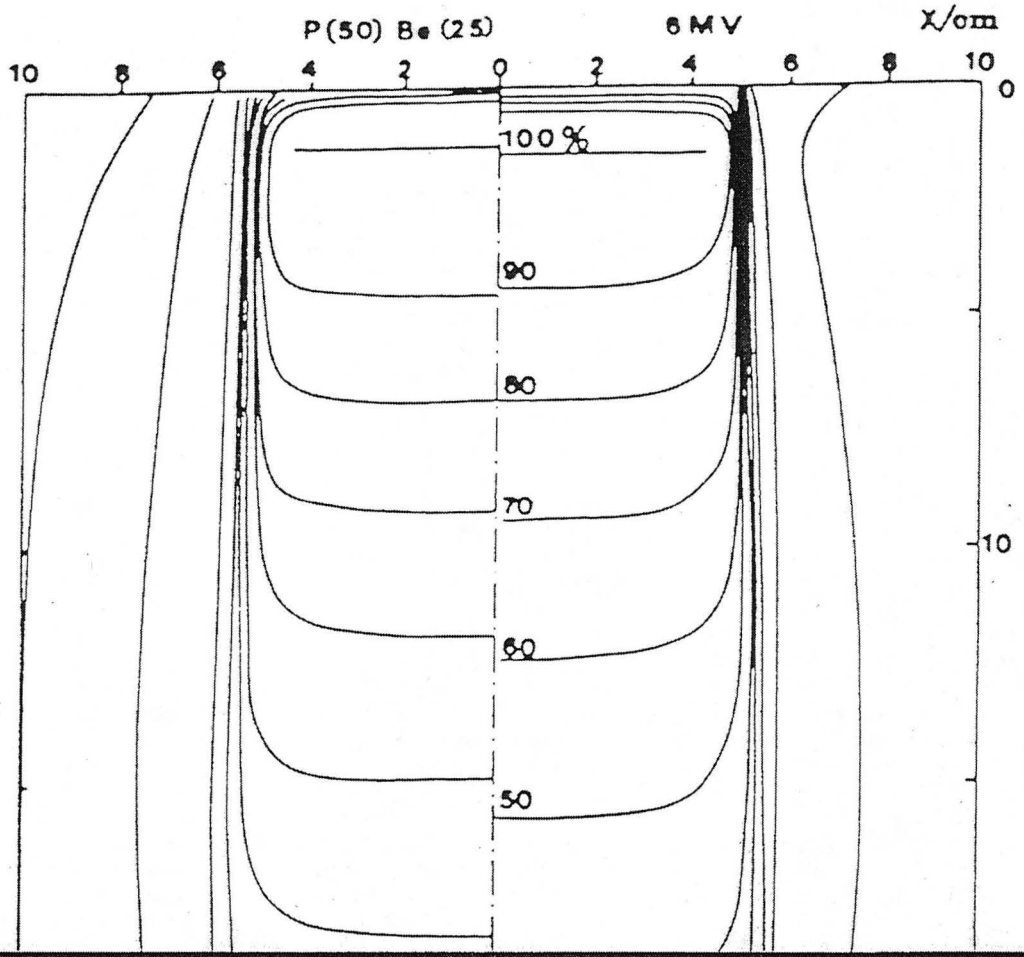
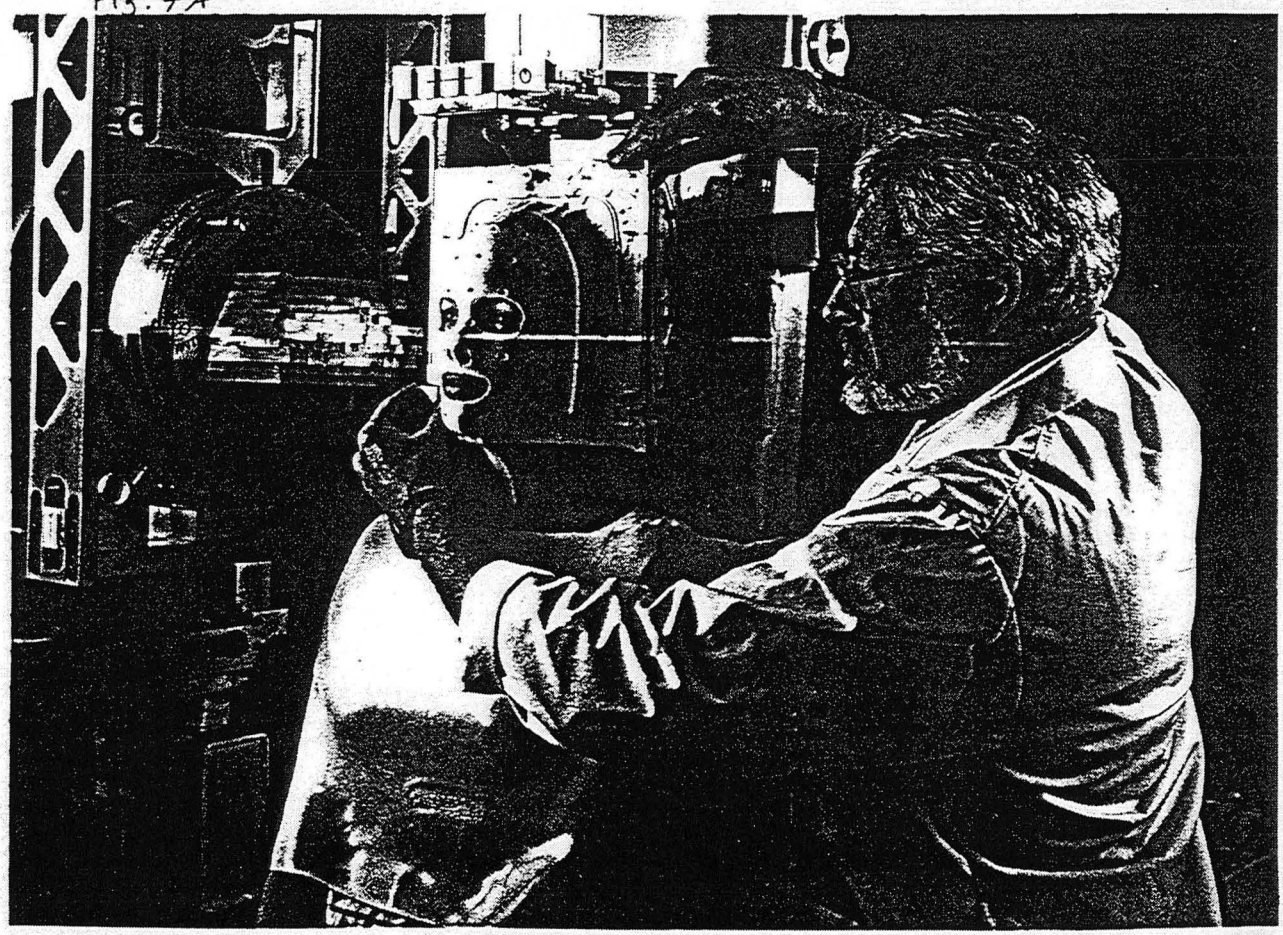


Fig. 6

Fig. 7A



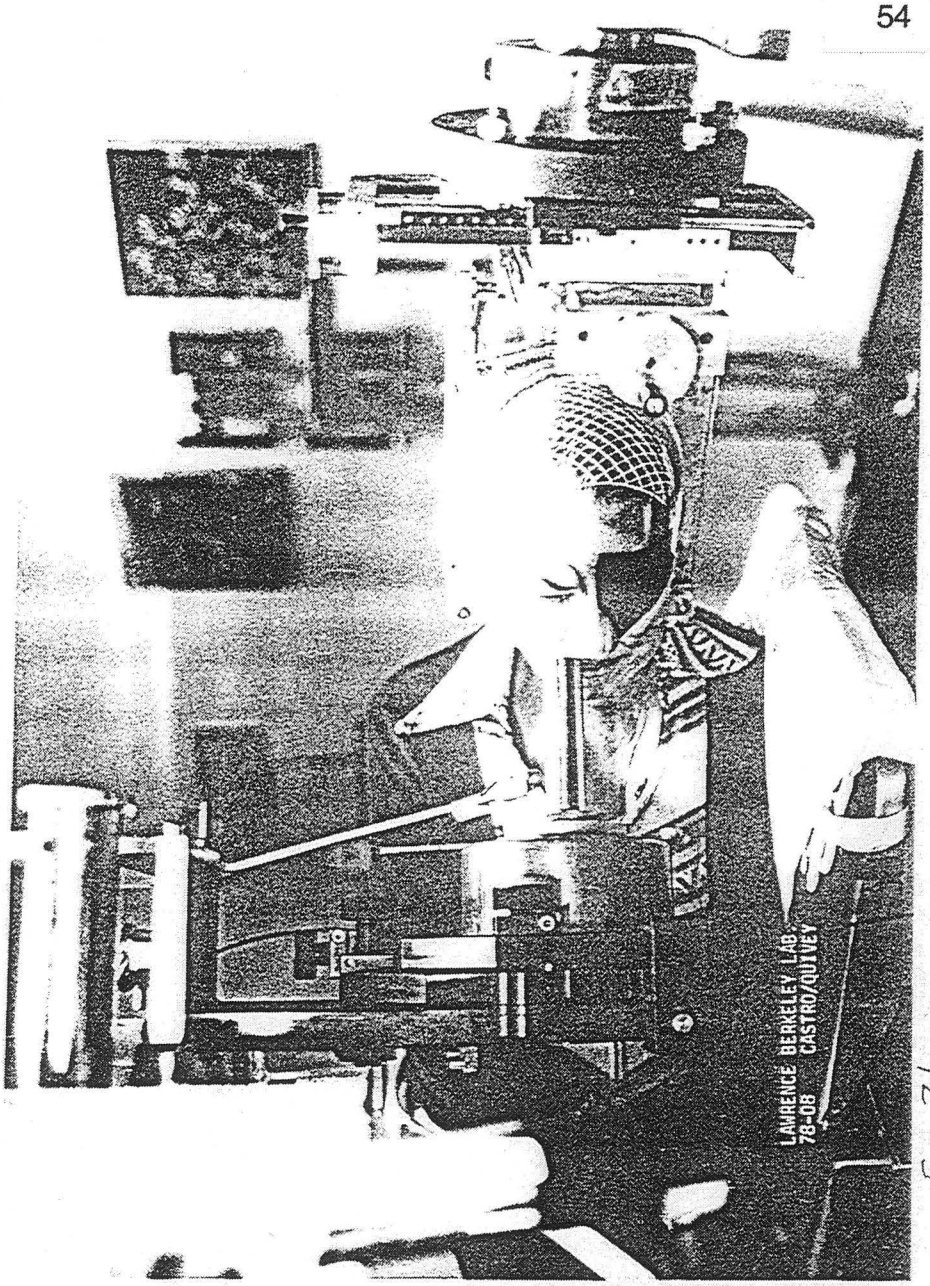
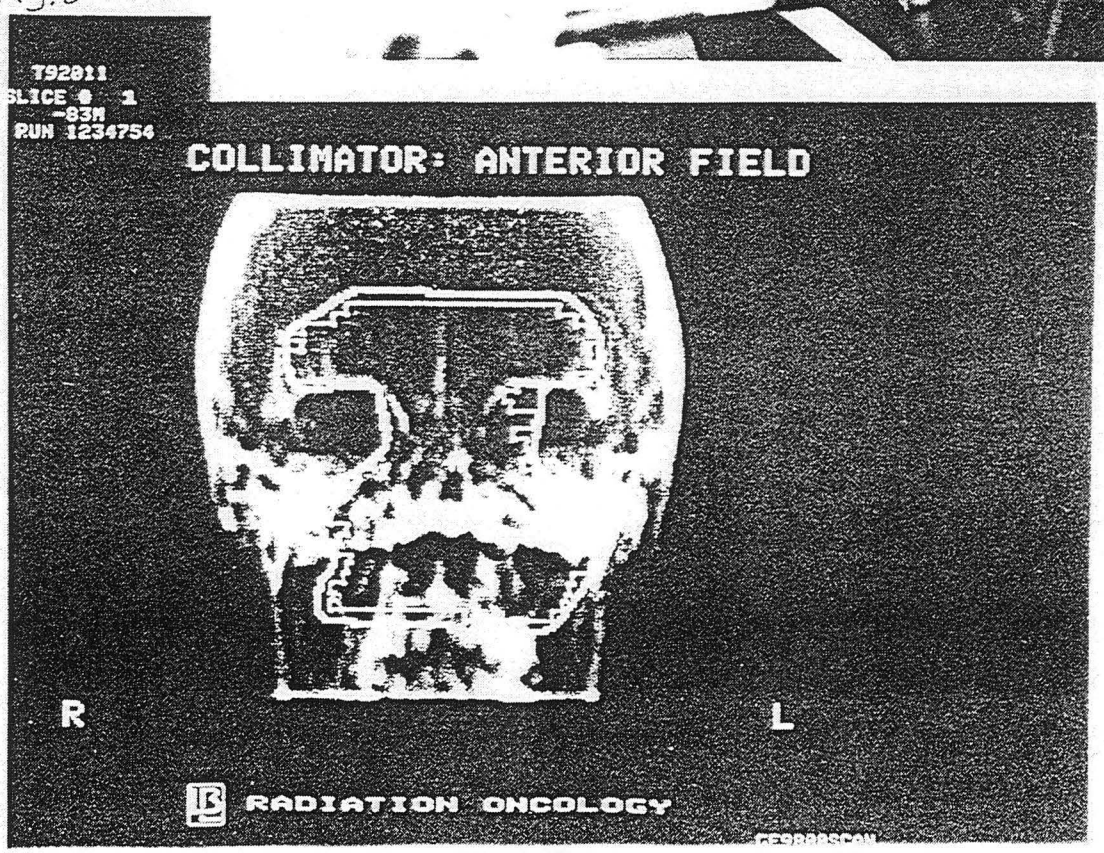

LAWRENCE BERKELEY LAB
78-08 CASTRO/QUIVEY

Fig. 7b

Fig. 8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R
L
RADIATION ONCOLOGY

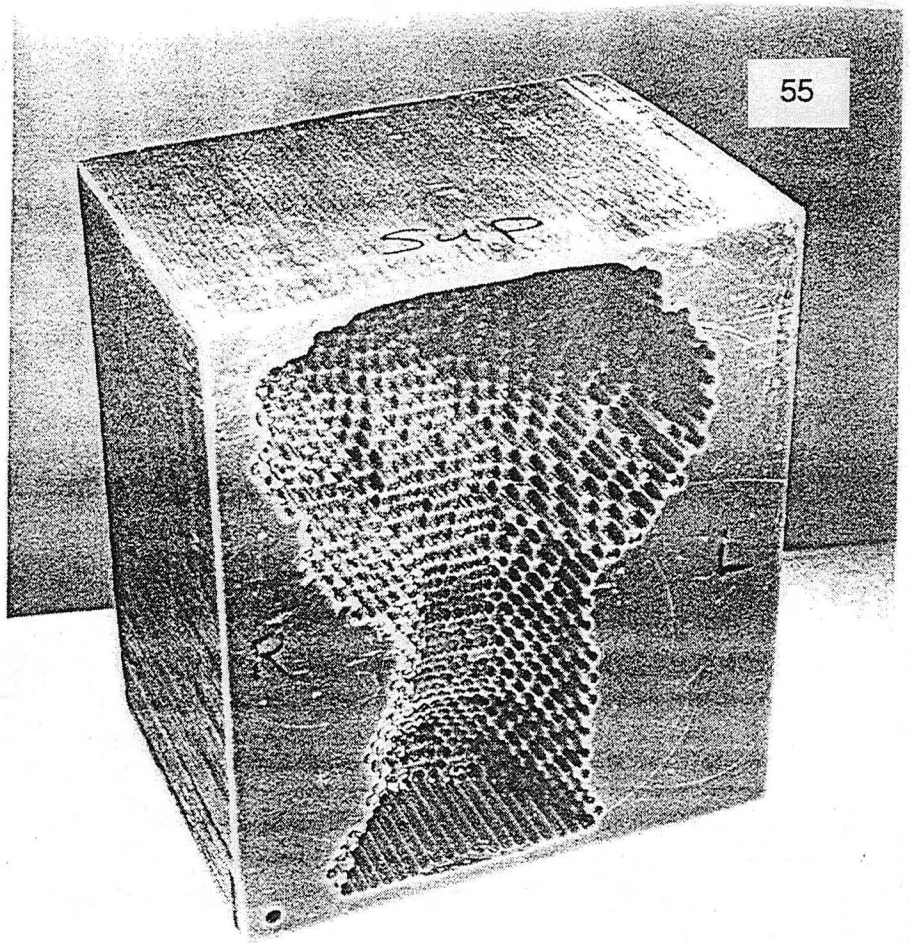
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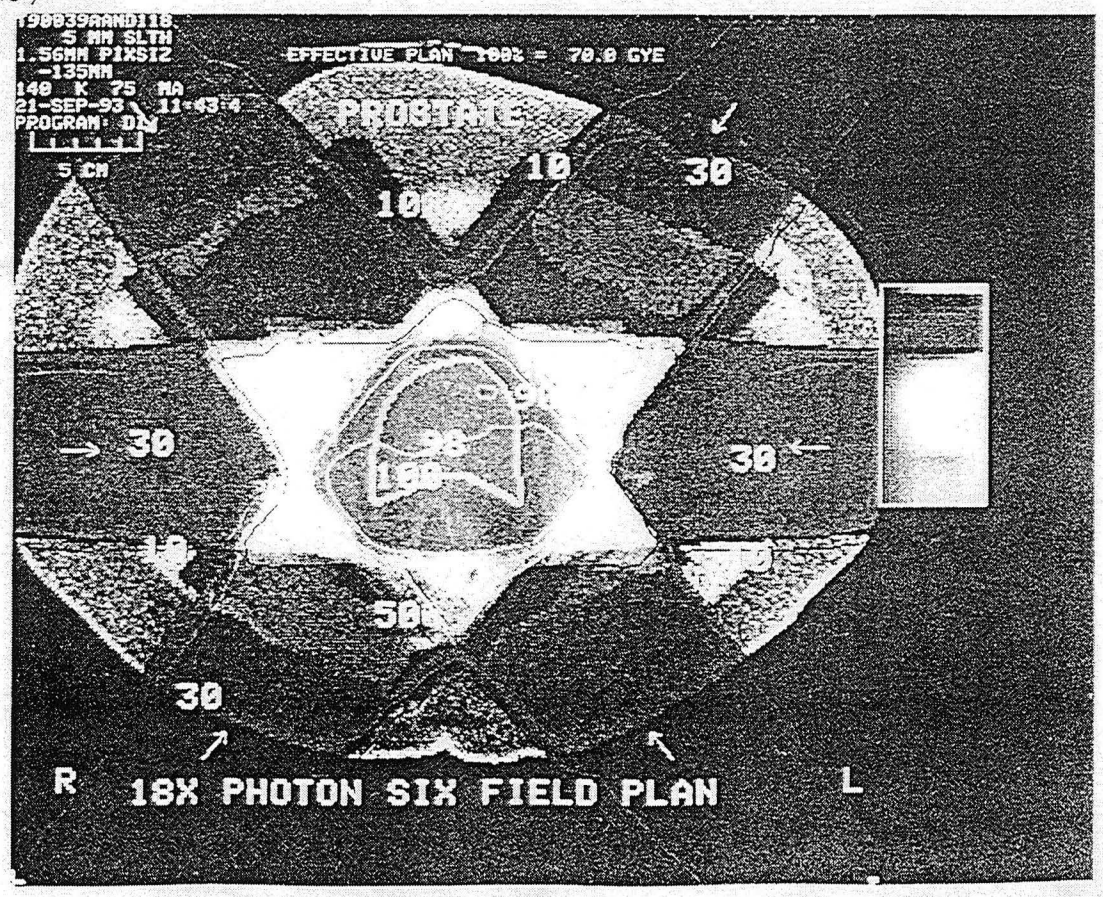
fig. 9

Fig. 10A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140 K 75 MA
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10
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50
R
18X PHOTON SIX FIELD PLAN
L

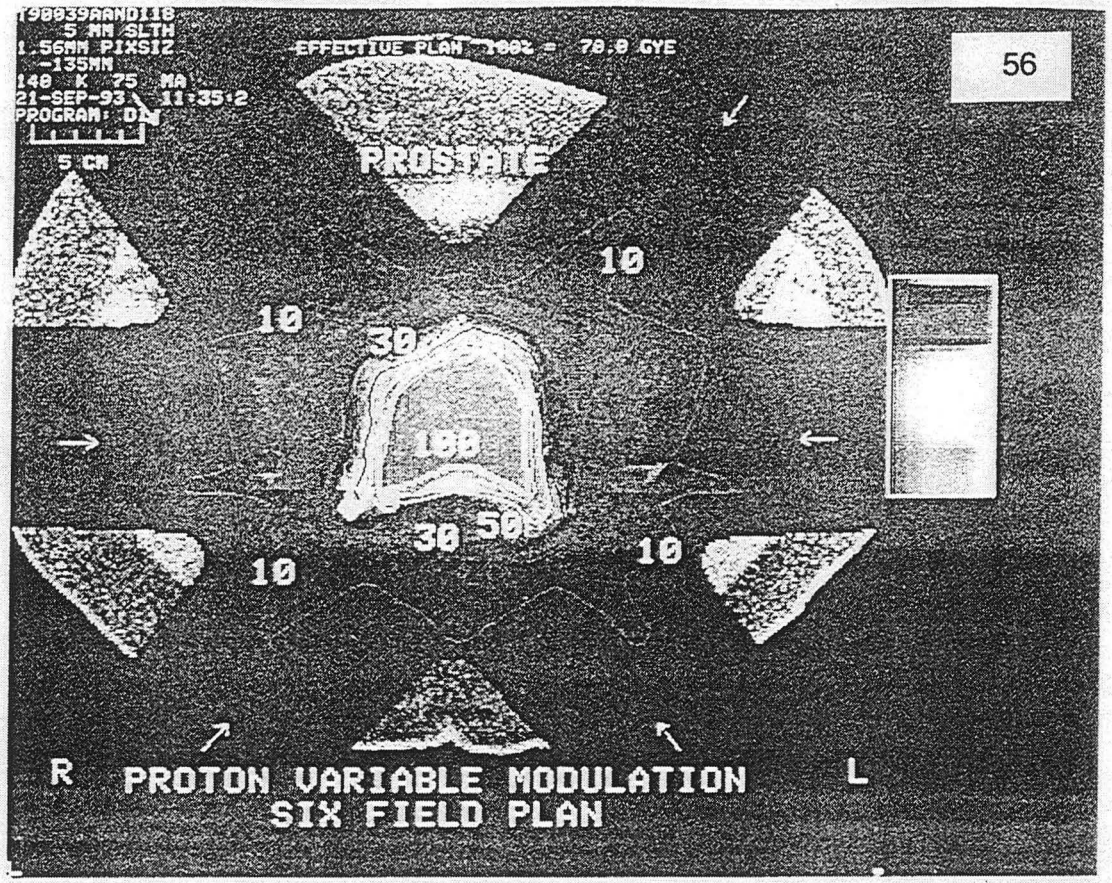
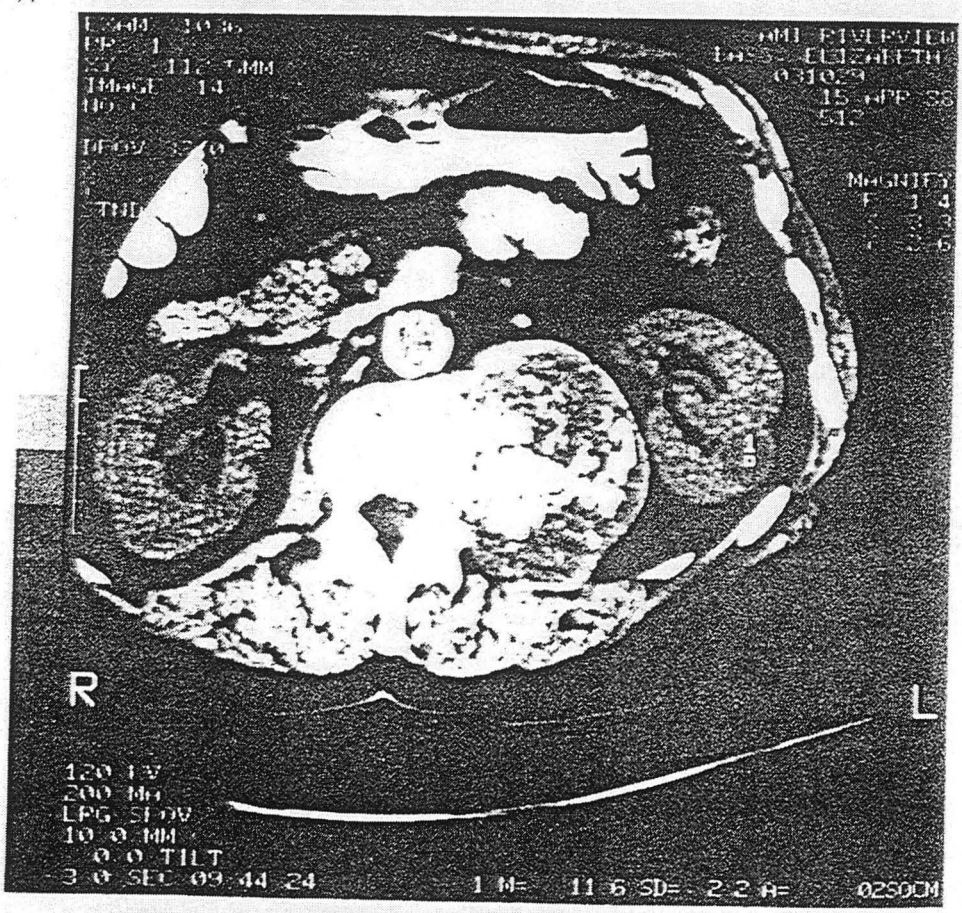
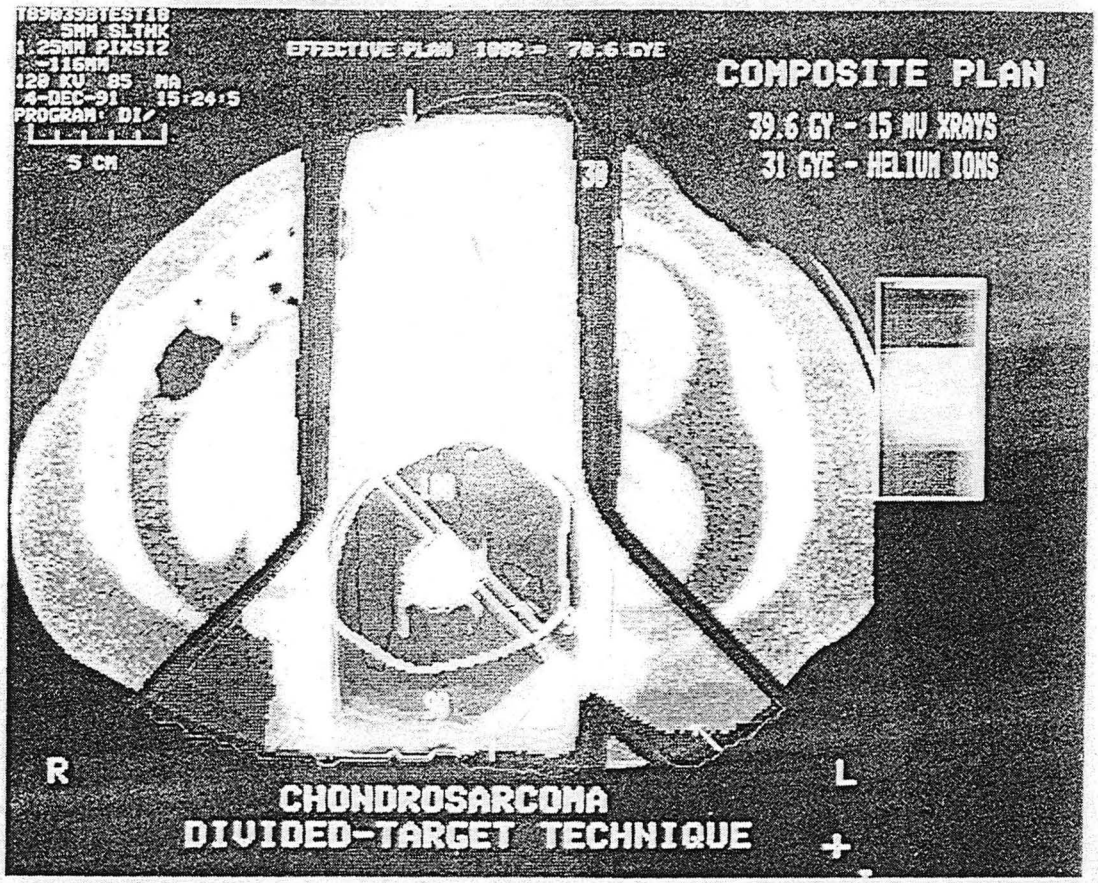


Fig. 10b

Fig. 11A

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EFFECTIVE PLAN
COMPOSITE PLAN
39.6 GY - 15 MV XRAYS
31 GYE - HELIUM IONS
R
L
CHONDROSARCOMA
DIVIDED-TARGET TECHNIQUE

Fig. 11b

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