APPLYING CHARGED PARTICLE PHYSICS TECHNOLOGY FOR CANCER CONTROL AT LOMA LINDA UNIVERSITY MEDICAL CENTER, USA

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Abstract

The world's smallest proton synchrotron soon will begin to be used for patient treatments at Loma Linda University Medical Center in the United States, as part of an effort to apply and exploit high-energy physics technology for cancer control. Proton therapy has superior characteristics to accomplish this end, notably a dose distribution that facilitates the delivery of effective doses while sparing adjacent tissue. The characteristics are exploited in a synchrotron, designed and built in a cooperative effort among university, government and industry investigators, for treating patients. The characteristics and implications of this development are discussed.

Introduction

The precision of proton therapy underlies its clinical application. Exploiting that precision to its fullest, underlies the effort to apply high-energy physics technology for controlling cancer at Loma Linda University Medical Center. The classic intent of radiation oncology is to treat only diseased tissue, sparing normal tissue in the process. In practice, this ideal is often compromised so that all areas of risk may be encompassed. Normal tissue tolerances in those areas determine the dose that can be given; often, one insufficient to control a malignant tumor.

Because photons and electrons lose most of their energy near the point of entry, it often is difficult to concentrate a cancerocidal dose deep in the body. Photons and electrons also cause much secondary lateral scatter; surrounding normal tissues receive part of the dose, resulting in side effects. Attempting to circumvent these problems, radiation oncologists often irradiate the tumor through several portals with overlapping beams, building up the target volume dose and minimizing the dose to normal tissues. Using such strategies with protons, one can deliver higher doses of ionizing radiation with even greater precision.

The Clinical Problem

According to current information from the American Cancer Society,[1] more than one million Americans will develop some form of non-skin cancer in 1990. About three of every ten Americans will develop some form of cancer at some time in her or his life, and cancer affects three of every four families in some way. Among Americans receiving treatment for cancer localized to an anatomic region and theoretically amenable to control by locoregional therapies, disease, failure to control the local process occurs in 225,000 cases every year.[2] In addition, morbidity from disease and treatment causes unacceptable suffering in uncounted numbers of people. Such data give impetus to the search for more effective locoregional treatments.

History of Proton Therapy

The first proposal for the medical use of protons occurred in 1946, when Robert Wilson published his landmark paper.[3] Because protons deposit almost all their energy at any desired depth in the body, Wilson believed that patient trials should be undertaken on the accelerators then being built for high-energy physics research.

In the mid-1950's, proton beams were first employed on humans; 26 patients received pituitary irradiation for advanced breast cancer.[4,5] The second application of a physics research accelerator for proton therapy occurred in Sweden in 1957; by 1968, 69 patients had been treated[6,7] Physicians working with Harvard Cyclotron Laboratory began employing a 160 million electron volt (MeV) proton beam for therapy in the early 1960's; pituitary adenomas were among the first tumors treated.[8,9] Large field radiation therapy began at Harvard in 1974, as the applications of the superior physical dose distribution of the proton beam to a range of tumors became apparent.[10-12] Proton beam therapy began in the Soviet Union in the mid-1960's;[13] the Japanese experience began in 1979, at Chiba; another facility opened at Tsukuba a few years later.[14] At the Paul Scherrer Institute in Villigen, Switzerland, proton beam therapy commenced in 1985[15].

Interest in proton therapy grew rapidly as results were reported from early investigations. As a means of consolidating this interest and directing it to optimize the clinical potential of the modality, the Proton Therapy Cooperative Group (PTCOG) was formed in 1985. This group meets semi-annually to report to its international membership on the state of the science; works to design therapy facilities for institutions around the world; and drafts protocols for analyzing proton treatment in a scientific, cooperative manner. Through its newsletter, PTCOG tabulates the progress of proton and other charged particle therapies in institutions employing physics research accelerators for medical purposes. Currently, over 8,000 patients have been treated with protons in these and other institutions around the world.[16]

A Superior Beam for Clinical Radiation Therapy

Like conventional external beam iradiation, proton radiation therapy is directed to a tumor or other disease process, causing changes which kill irradiated cells or render then unable to function. In terms of their relative biologic effect (RBE), protons are similar to photons (the RBE of protons is generally accepted as being approximately 1.1, compared to cobalt).

A proton beam has almost no secondary lateral scatter and deposits most of its energy at the Bragg peak; little energy is deposited along the path until the peak is reached, and virtually no energy is deposited distal to it. By spreading out the Bragg peak through energy variation or other measures, the radiation oncologist can encompass the target volume.

Such precision means the radiation oncologist can increase the dose to the tumor while reducing the dose to surrounding normal tissues, allowing for higher tumor-destroying doses and a greater chance for locoregional disease control without stopping treatment because of side effects.

Demonstrated Effectiveness of Proton Therapy

Results from difficult-to-treat tumors show the benefits of the modality. Some ophthalmologists treat ocular melanoma, for example, by enucleation. Where protons or helium ions have been used, however, the cure rate is more than 95%, and most patients retain useful vision in treated eyes.[17,18] Pituitary tumors show similar results and, like small tumors of the eye, can be treated in one to three days on an outpatient basis.[19] Because of their proximity to the brain stem, tumors of the base of the skull are difficult to control. In contrast to conventional irradiation's control rates of 35% or less, proton and helium ion therapy have yielded control rates of approximately 85%, and patients can pursue daily activities after being treated.[20] Proton therapy has also been employed in non-cancerous processes, such as arteriovenous malformations of the brain.[21]

The precision of proton therapy has long been known, but applications have been limited because physics research accelerators were not designed for treating patients, and because many tumors could not be localized with the necessary precision. Since the mid-1970's, however, CT, MRI, SPECT, PET, ultrasound, improved conventional imaging modalities and improved means of contrast enhancement, have all increased the precision with which disease extent is defined. These improvements, combined with better understanding of the radiobiological effect of conventional and heavy charged particle irradiations, justify the expense and effort required to build a proton accelerator and facility designed for patient treatments.

Designing a Proton Accelerator for Medical Use

The Loma Linda accelerator is the smallest synchrotron in the world. It was designed from the start to be a patient-treatment machine, and reflects the input of physicians, physicists and engineers from around the world, via the efforts of PTCOG, which drafted its specifications, Fermi National Accelerator Laboratory, which designed and built it, and Science Applications International Corporation, which assisted in the design and installation at Loma Linda, and will market future, similar accelerators.

The requirements for a medical accelerator differ from a high-energy physics research accelerator. For example, the ability to vary the energy is critical, in order to encompass the varying anatomical configurations of tumors. A medical machine also must be simple to operate and easy to maintain, in contrast to one employed in a high-energy physics laboratory. Some of the characteristics of the Loma Linda synchrotron are indicated in Table 1.

Table 1
LLUMC Accelerator; Goals of Design

Energy	70-250 MeV
Beam spill time	0.05-9.9 sec
Cycle time	2 sec.
Beam intensity	1 E 11 protons/pulse
Ion source	Duo-plasmatron 100 mA max. current 70 mA operational 30 kV
Linear accelerator	RFQ 2 MeV 20 microsec. pulse 20 mA output current
Synchrotron	Zero gradient Betatron tunes: @ extraction .5/1.36 @ flattop .6/1.30 Harmonic: 1 Single turn injection 20.05 meter circumf. Inject above transition Cycle time: 2,4,8 sec. Aperture: 5 x 10 cm. Extraction: 0.4-10 sec.

Expected Applications

Computer simulations show the benefits that can be expected when the modality is employed. In locally advanced cancer of the uterine cervix, for example, control is difficult to achieve with conventional irradiation because the needed large fields and high doses result in unacceptable doses to nearby vital structures. Proton beams will enable delivery of even higher doses, while still avoiding the nearby structures. The ability to spare the opposite parotid gland and mandible, while delivering high doses to tumors of the tonsillar region, suggests a role for proton therapy in such malignancies staged T2 or higher. In a series of carefully planned protocols, the patients who can benefit from proton therapy will be identified. As suggested in Table 2, it is expected that such studies will reveal several groups of patients who will benefit.

Table 2
Anatomic Sites of Potential Application

CNS	Glioma; meningioma; cervical chordoma and chondrosarcoma; pituitary adenoma; acoustic neuroma; craniopharyngioma
H & N	Oropharynx; nasopharynx; larynx; hypopharynx
Thorax	Esophagus; lung
Abdomen	Pancreas; retroperitoneal soft tissue sarcoma; para-aortic nodes
Pelvis	Bladder; uterine cervix; prostate; unresectable or recurrent colo-rectal or endometrial carcinoma
Pediatric	Optic & brain glioma; pineal malignancies; Hodgkin's disease; retinoblastoma; medulloblastoma; rhabdoblastoma; neuroblastoma
Other	Hodgkin's, non-Hodgkin's lymphoma; soft tissue sarcoma; arteriovenous malformations

Initial Endeavors

Opening in 1990, the Loma Linda proton therapy facility is eventually expected to serve between 1000 and 2000 patients annually. The first patients will be treated with the stationary beam this autumn, with one of the gantries commencing operation the following winter. Patients with eye and head & neck tumors will be treated first, with the stationary beam. Patients with tumors in other anatomic sites will be treated with the movable beam. One of the three gantries will be commissioned in winter, 1991, for this task. Experience with that gantry will be utilized for modifying the other two, if needed.

The Loma Linda facility will be a worldwide resource for research and learning about proton beam therapy. Researchers will investigate topics such as: dose escalation and time de-escalation protocols; radiobiologic effects of particle therapy; the physics and engineering of proton accelerators; simulated effects of outer-space radiation; and combined treatment modalities. A charged-particle database is being developed to assist in these efforts, and satellite and microwave communications systems will enable physicians to send patient images to LLUMC for therapy planning. Data generated by these studies will be made available to the general medical community, and will help physicians and patients determine whether proton therapy might be advantageous for them.

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