The Promise of Proton Therapy is Two-fold—
Less toxicity and higher cure rates than achievable with X-ray therapy

by Nancy Price Mendenhall, MD

Benefits of Proton Therapy

In most cancers requiring radiation therapy, proton therapy can produce better radiation dose distributions with respect to cancer and normal tissue than techniques employing X-rays. A better radiation dose distribution is more important in some clinical situations than others. When considering possible benefits of proton therapy, it is useful to consider the therapeutic ratio likely with other radiation therapy treatment options first—i.e., the probability that other radiation options will control the tumor without causing toxicity.

In some cancers, proton therapy is the only treatment option, offering hope for cure without unacceptable toxicity. Examples in this category include chordomas and chondrosarcomas occurring at the base of the skull. Because of proximity to critical structures such as the brainstem and optic nerves, surgery alone is rarely successful and sufficient radiation doses to destroy these tumors usually cannot be given with X-ray therapy. However, clinical researchers at Harvard have reported excellent long-term disease control with minimal toxicity with proton therapy.[1-3]

In a second group of cancers, other treatment options are available, but the therapeutic ratio of these other options leaves room for improvement in either tumor control or normal tissue toxicity. In these cases, clinical or dosimetric data suggest an important and likely measurable benefit of proton therapy. One example is melanomas of the eye, which can be treated with surgical removal of the entire eye, radiation with a cobalt plaque, or proton therapy. Large clinical trials from the U.S. and England show similar survival rates among the three treatment options, but better long-term preservation of vision with proton therapy.[4]

A second example is pediatric tumors, in which even low radiation doses to normal tissues cause measurable effects on neurocognitive function, muscle and bone growth, endocrine function, etc., so any savings in normal tissue exposure from proton therapy is likely to produce measurable benefits.

A third example in this category is early stage prostate cancer where there is room for measurable improvement in disease control, but not at the price of additional toxicity.[5] The improved dose distribution achieved with proton therapy was used to test the concept of radiation dose escalation as a means of decreasing tumor recurrence.[5] Prostate cancer patients were randomized to receive proton therapy to two different doses after initial treatment with conventional radiation therapy. Patients receiving the higher dose with protons had only half the number of PSA tumor recurrences as those receiving the lower dose, but no increase in toxicity because of the avoidance of normal tissue possible with proton therapy.

In a third group of cancers, the therapeutic ratio with conventional irradiation is high, and the dosimetry benefits from proton therapy may not translate into measurable clinical improvements. An example may be early stage breast cancer treated with breast conserving surgery and conventional radiation therapy, where both the local recurrence and toxicity rates are very low.

Proton therapy has now been used with success in prostate cancer, eye tumors, sarcomas, base of skull tumors, brain, lung, head and neck, gastrointestinal, and pediatric cancers.

How Proton Therapy Is Delivered

Protons are generated from water that has been de-ionized. Water is comprised of two atoms of hydrogen and one atom of oxygen. When an electric current passes through water, the water undergoes electrolysis and is broken into its parts, hydrogen and oxygen, both components of the air we breathe. The hydrogen is then injected into the cyclotron, where high heat creates a plasma state in which electrons can be stripped away from single hydrogen atoms by an electric field, creating a stream of protons.

The cyclotron, which may weigh 440,000 pounds, accelerates protons to increasing speeds by alternating electromagnetic forces (see Figure 1. Proton Beam Therapy Blueprint). Once the acceleration of the protons reaches the

University of Florida Proton Therapy Institute (UFPTI) is a three-story facility of approximately 98,000 square feet. Within UFPTI is a conventional radiation therapy suite with three treatment vaults; a simulation suite including an MRI, a CT scanner, and a PET/CT scanner for tumor localization and treatment planning; the proton therapy suite; space for future bench research, as well as faculty and staff offices.

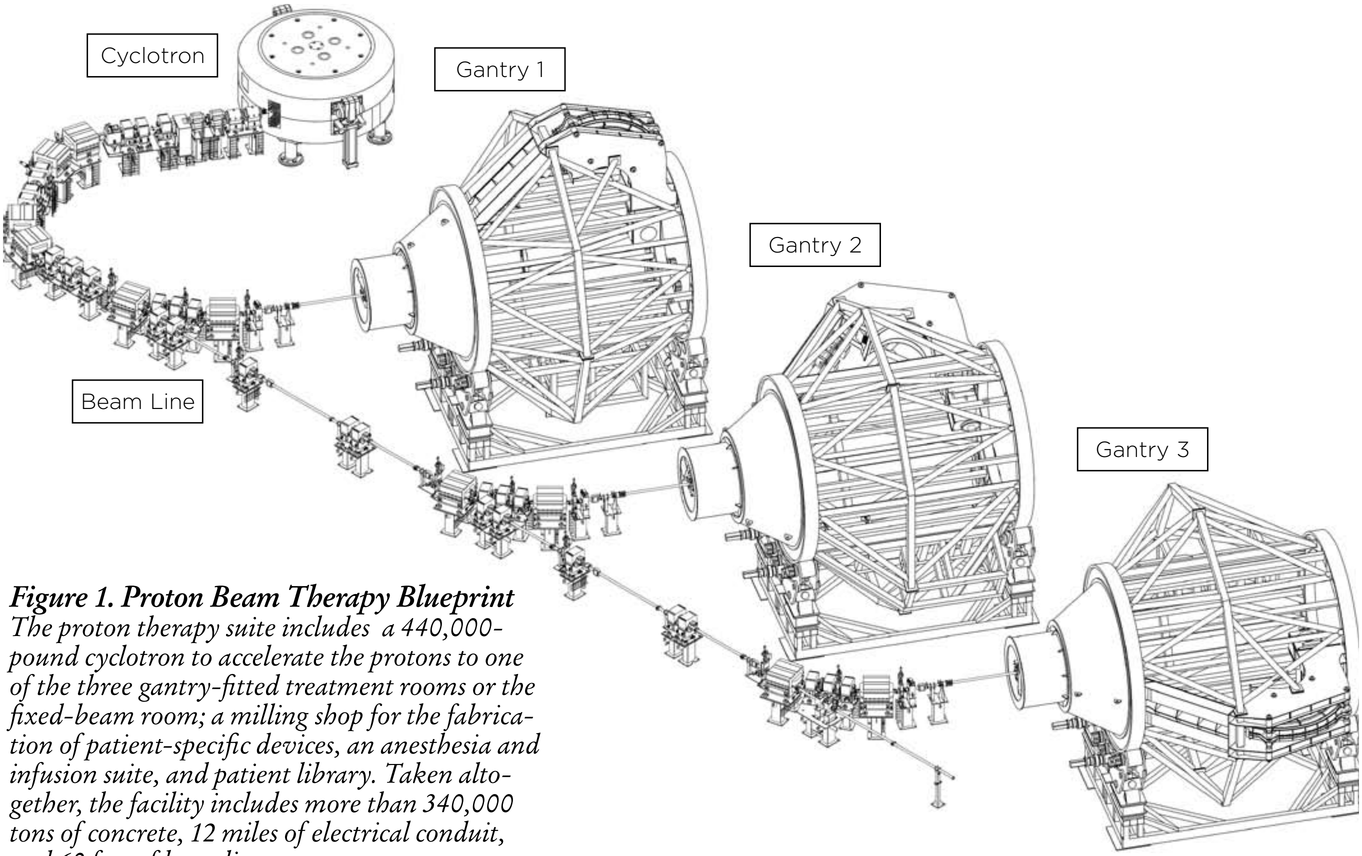

Figure 1. Proton Beam Therapy Blueprint
The proton therapy suite includes a 440,000-pound cyclotron to accelerate the protons to one of the three gantry-fitted treatment rooms or the fixed-beam room; a milling shop for the fabrication of patient-specific devices, an anesthesia and infusion suite, and patient library. Taken altogether, the facility includes more than 340,000 tons of concrete, 12 miles of electrical conduit, and 60 feet of beamline.

desired energy (230 MeV to 250 MeV), magnets are used to direct the protons into a beam line that carries the protons into treatment rooms. The protons may be directed into a fixed horizontal or vertical beam line or into a 360-degree rotational gantry that can deliver the beam of protons to a target from any angle. The gantries tend to be large, requiring up to three stories of space and weighing up to 100,000 pounds. The patient is positioned on either a treatment table or in a treatment chair to receive treatment. Modern treatment tables have up to six degrees of freedom facilitating submillimeter precision in patient alignment.

Proton Therapy vs. Conventional Radiation Therapy

A true comparison between these two technologies will measure four important areas: clinical outcomes, consistency in quality assurance, cost, and availability.

Although more than 40,000 patients worldwide have been treated with proton therapy, much of the experience has been in research facilities suitable for treating only a few rare tumors. Limited capacity for proton therapy in clinically dedicated facilities has prevented large-scale trials of proton therapy, but available data suggest that improved radiation dose distribution will translate into clinical advantages over other forms of radiation therapy in most cancers, where outcomes with conventional radiation therapy leave room for improvement.

The more radiation dose distributions are restricted to the actual targets, the more demanding the quality assurance measures. The treatment process with proton therapy requires onsite high-resolution imaging to define the three-dimensional target volume, highly sophisticated computerized treatment planning software, specialized patient immobilization devices, strategies to decrease movement of organs within the body during treatment, and submillimeter precision in patient positioning and beam guidance. The added precision requires additional physics and engineering personnel for technical support.

The cost of proton therapy is somewhat more than the cost of conventional radiation therapy, related to more expensive equipment and technical personnel required for treatment and equipment maintenance. With respect to capital cost, the price for a proton therapy facility that could treat 150 patients a day could be up to 10 times the cost of a conventional therapy facility with similar capacity. Proton therapy facilities are built to last a minimum of 30 years, however, while conventional linear accelerators require replacement after 7 to 10 years. Proton facilities also carry somewhat higher operational costs related to the level of expertise required for treatment planning, quality assurance, machine operation, and maintenance. Despite the higher initial costs of proton therapy, if proton therapy fulfills the promise of decreasing recurrence rates and toxicity rates, then its long-term cost may actually prove less than conventional radiation therapy. Medicare and most national health insurance companies provide coverage for their policyholders.

Since opening in August 2006, the University of Florida Proton Therapy Institute has delivered more than 4,000 proton therapy treatments. At UFPTI there are ongoing trials in a variety of head and neck cancers, brain tumors, pediatric malignancies, prostate cancer, and bone and soft tissue sarcomas.

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How Proton Therapy Works

Protons are subatomic particles considered by scientists for decades to be one of three basic building blocks of matter. Protons and neutrons make up the nucleus or center of atoms, while electrons, which have a negative charge, circle in orbit around the positively charged nucleus. Protons are 1,800 times more massive than electrons and have a positive charge, while neutrons are slightly heavier than protons and have no charge. Physicists have discovered even smaller particles, but it is the number of protons in the nucleus that distinguishes different types of matter. For example, oxygen is an element comprised of atoms which have eight protons, eight neutrons, and eight electrons, whereas hydrogen, another element in air, is comprised of atoms with only one proton, one electron and no neutrons.

Radiation therapy destroys cancer cells by causing chemical reactions known as ionizations, which lead to cell damage and ultimately to cell death. These chemical reactions occur when an electron is ejected from its orbit around a nucleus, either when the energy from an X-ray is absorbed or the electron is hit by a particle such as a proton. The atom then has fewer electrons than protons, and thus becomes a positively charged ion. The electron attaches to another atom or molecule which then becomes a negatively charged and highly active ion. This interaction occurs in both cancer cells and normal tissue cells, so radiation can kill cancer cells but also cause damage to normal tissues.

Most therapeutic radiation today is given with X-rays generated by linear accelerators. When X-rays pass through tissue there is a characteristic pattern of energy absorption, which is most intense between 1 and 5 cm below the skin surface (see Figure 2), but continues with most of the radiation exiting from the patient.

The process in proton radiation is similar: when protons collide with atoms, ionizations occur leading to cell damage or death. However, unlike X-rays, protons can travel only a finite distance, because they have mass. The faster protons are accelerated, the farther they travel. As they enter tissue, they collide with occasional atoms. Because they are relatively heavy compared with electrons, they lose a small amount of energy and slow with each collision, in contrast to X-rays which are completely absorbed on collision. Just before the protons reach the end of their range, they deposit the majority of their energy. This peak of energy deposition is called a Bragg peak (see Figure 3).

The important therapeutic difference between X-rays and protons is related to the difference in the pattern of energy (or radiation dose) deposition, (see Figure 2). In general, an X-ray beam is like a bullet, which passes through a patient, leaving a track of damage from entrance to exit that is most intense just below the skin surface. A proton beam loses much less dose as it enters tissue, then deposits a very high relative dose just before it stops. Since the protons stop, there is no exit dose. The depth protons travel in tissue is directly correlated with their speed, so by accelerating protons to a specific energy, one can set the precise depth at which most of the radiation energy will be deposited. In contrast to X-rays, a proton beam is like a firecracker which can be set to go off exactly at the tumor.

Because, most of the energy with X-rays is actually deposited in normal tissues the X-ray beam encounters before reaching the tumor and in tissues the X-rays pass through as they exit the patient, there is much more radiation inadvertently given to normal tissues with conventional X-ray therapy than with proton therapy. This

Figure 2. X-Ray and Proton Dose Distribution

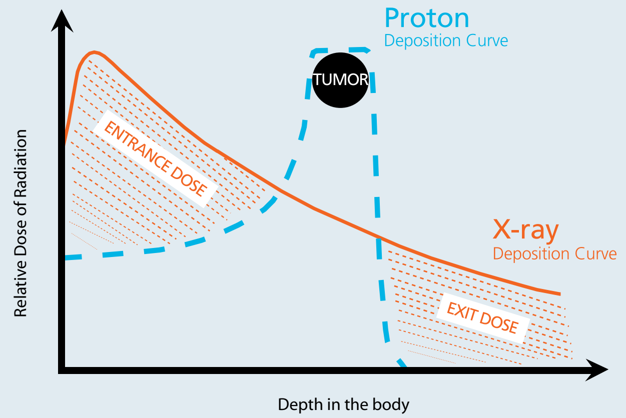
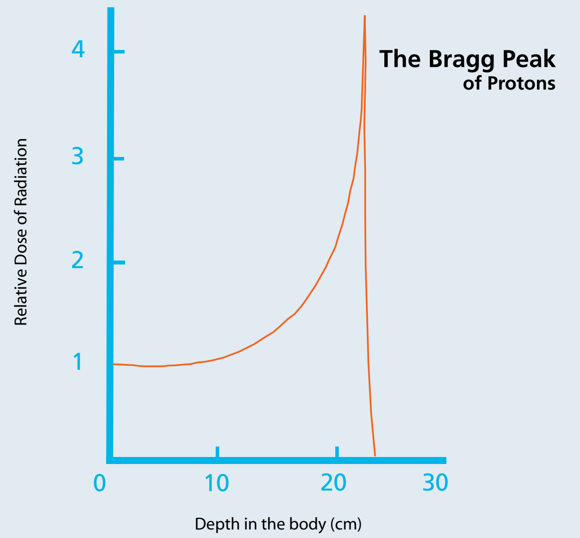


Figure 3. Bragg Peak of Protons



means there is generally a higher risk of damage to normal tissues with X-rays than with protons, so the use of proton therapy is likely to significantly reduce the risk of treatment complications. As a result of normal tissue at risk, the radiation dose that is given to the tumor is often compromised to avoid normal tissue injury.

The choice of radiation dose is usually a compromise between the ideal dose to eradicate a tumor and a dose that is unlikely to cause particular complications in normal tissues around the tumor. Because less damage is done to normal tissues with protons, it will be possible to deliver higher doses to tumors, likely resulting in higher cure rates. So the therapeutic promise of proton therapy is two fold: higher cure rates and fewer complications.

A Brief History of Proton Beam Therapy

Proton therapy, a type of radiation treatment for cancer, is generating much interest across the U.S., as well as in Europe and Asia. Although proton therapy was first used for patient care in 1954, it was not until 1991 that the first proton facility dedicated to patient care opened at Loma Linda University Medical Center in California. Another decade went by before the second such facility in the U.S. opened in 2001 at the Massachusetts General Hospital. In 2004, the Midwest Proton Therapy Institute in Bloomington, Indiana adapted an extant research cyclotron to clinical usage. In 2006, $100-million-plus proton therapy centers opened at the M. D. Anderson Cancer Center in Houston and the University of Florida in Jacksonville. Across the world, only 23 cancer centers offer proton therapy, some with technical limitations that preclude treatment of certain types of cancers. Recently a number of other major academic and community cancer centers have announced intentions to build proton therapy facilities.

The recent increased interest in proton therapy is related to recognition of the applicability of proton therapy to many kinds of cancers and the demonstration of an economically feasible method of proton treatment deliverable in the clinical setting. In 1991, Loma Linda University opened the first clinically dedicated proton therapy facility with the development of a rotational gantry similar to those used in conventional X-ray therapy systems, which permitted proton delivery from any direction, significantly increasing the applicability of this modality. Over the next decade, the feasibility of using proton therapy in a variety of malignancies was demonstrated by Loma Linda University Medical Center and other facilities outside the U.S.

This more general experience complemented the excellent outcomes already documented in rare tumors such as melanomas of the eye and chordomas at the base of the skull that had been treated in research centers around the world, including Massachusetts General Hospital. The *JAMA* 2005 publication of a randomized controlled trial conducted by Loma Linda University Medical Center and Massachusetts General Hospital comparing two dose levels in prostate cancer treated with proton therapy highlighted the utility of protons for prostate cancer, the most common malignancy in the U.S., and proved the promise of proton therapy as a means of dose escalation to achieve higher cancer control rates without added toxicity.[5]

Meanwhile, in the background, the rapid proliferation of 3-D conformal radiation therapy, and subsequently IMRT, during the last decade set the stage for the development of a technical infrastructure to support proton therapy, which likewise relies on precise knowledge of the size, shape, and whereabouts of the tumor and more intensive physics engineering and technical support for treatment planning and delivery than necessary in conventional radiation therapy.