PROTON THERAPY:
AN OVERVIEW

ProTom International | 2018

PROTOM
proton therapy technologies

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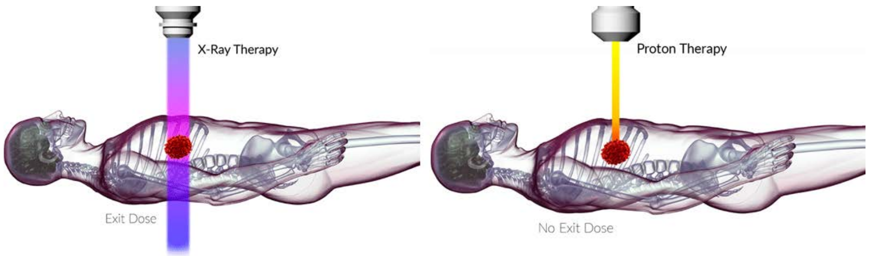
WHAT IS PROTON THERAPY?

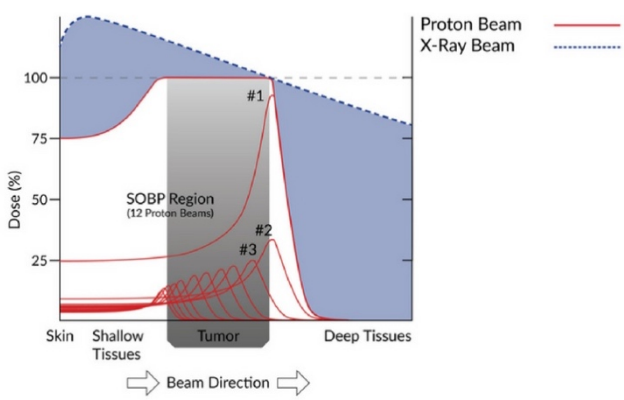
In the treatment of cancer, radiation therapy works by attacking a cancer cell's DNA, inhibiting growth and reproduction. While advancements in targeting have made the delivery of photon radiation more exact, it can damage nearby healthy tissue and organs. X-rays deposit their energy on the way to, and then beyond its target, necessitating administration of entry and exit doses.[1] This additional exposure can cause substantial side effects for patients.

Figure 1: Traditional radiation treatment has a relatively high entrance dose and exit dose. Proton therapy has a lower entrance dose and no exit dose.



Proton therapy, conversely, leaves healthy tissue undisturbed.[2] This distinct advantage comes from the unique behavior of protons as they move through the body. Demonstrated on the Bragg Curve, protons reach a peak near the end of their path. The absorbed dose of radiation increases very gradually with greater depth, rising to its peak when the protons are stopped. Highly-charged protons deliver a treatment dose more directly into targeted tissue and tumors than X-rays. In clinical applications, proton therapy can be administered to a precise depth within a patient's body, to a site as small as a few millimeters in diameter - leaving healthy cells unaffected.[3]

Figure 2: The Bragg Peak



[1] W.D. Newhauser, R. Zhang. The physics of proton therapy. *Physics in Medicine and Biology*. 60(8) (2015). doi:10.1088/0031-9155/60/8/r155
[2] X. Zhang, Y. Li, X. Pan, et. al. Intensity-Modulated Proton Therapy Reduces the Dose to Normal Tissue Compared With Intensity-Modulated Radiation Therapy or Passive Scattering Proton Therapy and Enables Individualized Radical Radiotherapy for Extensive Stage IIIB Non-Small-Cell Lung Cancer: A Virtual Clinical Study. *Int J Radiat Oncol Biol Phys.* 77(2):357-66 (June 12010). doi:10.1016/j.ijrobp.2009.04.028.
[3] T.P. Diwanji, P. Mohindra, M. Vyfhuis, et. al. Advances in radiotherapy techniques and delivery for non-small cell lung cancer: benefits of intensity-modulated radiation therapy, proton therapy, and stereotactic body radiation therapy. *Translational Lung Cancer Research*. 6(2), 131-147 (2017). doi:10.21037/tlcr.2017.04.04

HISTORY OF PROTON THERAPY

The field of radiation oncology has made significant strides since practitioners began using photon radiation therapy around the turn of the 20th century. Not until the 1950s, though, did researchers begin to recognize the full potential of isolating protons for the treatment of medical conditions. Advanced theoretical understanding of particle acceleration, proton beams, and their applied use in radiation treatment has improved outcomes for patients of many types of cancers.

The cyclotron, a type of particle accelerator, was first conceived by Ernest Lawrence in 1929. It was built at Berkley Radiation Laboratory at the University of California, Berkley. This initial research was focused not on the treatment of human malignancies, but on the discovery and exploration of particles and nuclear physics. In 1946, a Harvard particle physicist, Robert R. Wilson, proposed using proton beams for medical application. During his work collaborating with a team on the design of the Harvard Cyclotron Laboratory (HCL), he outlined the possible clinical applications of protons in a paper he titled “Radiological Use of Fast Protons.” Even with rapid technological advances, the basic tenets of Wilson’s paper still stand as the fundamental understanding of proton therapy over half a century later.

INITIAL CLINICAL APPLICATIONS

The first people to receive proton beam therapy were treated with pituitary irradiation, to control metastatic breast cancer, at Berkley Radiation Laboratory in 1954. In the years following the initial human treatments, more cyclotrons were built to establish proton therapy programs across the United States – Harvard University in 1961, the University of California, Davis in 1964, and the Los Alamos National Laboratory in 1974. The research from these facilities, coupled with the technological advances in proton radiation therapy and its delivery methods, have advanced proton therapy to its current position in the field of cancer treatment today. Proton therapy received U.S. Food and Drug Administration (FDA) approval in 1988. The first hospital-based proton therapy treatment center opened in California in 1991 – operating a modified, more efficient accelerator, called a synchrotron.

GROWTH OF PROTON THERAPY

Proton therapy has been used to treat more than 160,000 people worldwide. By 2030, it is estimated that between 300,000 and 600,000 patients will have received proton therapy treatment.[4]

A survey conducted by the National Association for Proton Therapy (NAPT) found the number of centers in the United States offering proton therapy more than doubled from 2012 to 2016 and that the number of patients receiving proton therapy treatment increased by 70% during this period.[5]

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[4] C. Pellizzon. Proton therapy – An evolving technology. *Advances in Modern Oncology Research*. 3 (2017). doi:10.18282/amor.v3.i4.245.

[5] National Association for Proton Therapy. Annual Survey Shows Surge in Cancer Patients Treated With Proton Therapy & in Number of Indications. March 26, 2018. https://globenewswire.com/news-release/2018/03/26/1453021/0/en/Annual-Survey-Shows-Surge-in-Cancer-Patients-Treated-With-Proton-Therapy-in-Number-of-Indications.html

In the United States, there are 28 active proton centers and 11 centers under construction or in the initial development stages.

PROTON THERAPY TECHNOLOGY

PARTICLE ACCELERATORS

Particle accelerators are used to deliver proton therapy, a type of radiation treatment that uses a beam of high-energy particles. Unlike traditional radiation therapy though, which utilizes photons (x-rays), proton therapy uses an intense beam of isolated protons.

Particle accelerators, used to manipulate the behavior of ions for use in treatment, play a central role in delivering proton therapies. The two types of accelerators most commonly used are the synchrotron and cyclotron. Oftentimes, these machines also represent the single largest expense for medical facilities. When determining what system best fits the needs of their constituency, medical facilities administrators and stakeholders should consider the unique features of each.

CYCLOTRONS

To achieve the acceleration of ions, a cyclotron employs a large, circular electromagnet and the application of oscillating voltage. When ions are initially injected into the center of the magnet, they begin traveling in a curved path. Upon experiencing the voltage, the ions take on more energy – causing the travel path to grow larger and the ions to spiral outward. The ions travel around their paths in the magnet at the same frequency as the voltage oscillates. As the ions achieve the desired level of energy, they travel on an orbit on the outermost edge of the electromagnet. It is at this point the ions can be extracted for treatment.

The determining factor of ion depth penetration is energy. For ions to reach treatment sites deep within the body, ions require more energy. For surface-level treatment sites, ions require lower energy. To treat sites with lower energy than the full energy of extraction, ion beams are passed through an energy degrader when the beam's energy is reduced.

The energy degrader presents significant and unique challenges for treatment facilities. When a beam is passed through the degrader, secondary scatter radiation is produced. Large and costly shielding walls, sometimes as much as 15 feet thick, are required in order to protect against the cyclotron's undesired output of scatter radiation. This can have a significant impact on the cost required to run and maintain the system. In addition, beam quality degradation – which may happen when beams are passed through the energy degrader – can lead to less precise targeting for treatment sites.

SYNCHROTRONS

Like cyclotrons, synchrotrons also use electromagnets to bend the ions while an oscillating voltage accelerates them. Unlike a cyclotron, the frequency of the oscillation and the strength of the magnetic field are not constant, but rather are ramped synchronously from a lower level to values that correspond the desired energy. Once the desired energy is reached, the ions are extracted and delivered for use in treatment.

Because an energy degrader is not required, use of the synchrotron eliminates many of the cyclotron's disadvantages. Synchrotrons have low secondary neutrons and scatter radiation, which lowers the risk of unnecessary and unwanted radiation to the patient and facility. Additionally, by scaling beam energy up to meet the required dosing, rather than scaling down as the cyclotron does, the synchrotron is the more energy efficient choice of the two particle accelerators. Add to that the cost savings of thick shielding wall installation and an easier installation, and the synchrotron becomes the top choice for proton therapy facilities.

BEAM DELIVERY

There are three types of proton-beam delivery methods: passive scattering, uniform scanning, and pencil beam scanning. When identifying treatment options and developing treatment plans, it is important to consider the method of proton-beam delivery. Pencil beam is the most modern form of delivering proton beams to patients.

PENCIL BEAM SCANNING

Pencil beam scanning (PBS) is the most precise form of proton therapy. Using an electronically guided scanning system and magnets, PBS delivers proton therapy treatment via a proton beam that is just millimeters wide. With PBS, beam position and depth are able to be controlled, allowing for highly precise deposition of radiation to be delivered in all three dimensions of the tumor.

ADVANTAGES OF PENCIL BEAM SCANNING

BEAM MODIFICATION

PBS does not require the use of patient-specific or field-specific devices (apertures, compensators) in the delivery of proton therapy treatment. This eliminates treatment delays, reduces treatment time, reduces costs, increases flexibility in treatment delivery, and reduces patient exposure to secondary radiation produced when the beam hits a device.

Delivery of proton therapy treatment with passive scattering or uniform scanning requires the use of patient-specific devices to conform the dose to the treatment volume. Unique devices are needed for each patient and for each treatment beam, because the shape of the tumor is unique to each patient, and because body composition can change during treatment, it is often necessary to create new devices over the course of treatment.

Whether the manufacturing of these devices occurs in-house or is outsourced, treatment cannot begin until the devices are in hand. When evaluating proton beam delivery methods, both treatment delays and costs related to device manufacture must be considered.
It is also important to consider the increase in treatment time and secondary radiation due to the use of the devices. As discussed above, it is necessary to use a different device for the delivery of each treatment beam. Switching devices for the treatment of each tumor field takes time, thereby increasing treatment time. Further, the secondary radiation that results increases the integral radiation dose to the patient. Neutrons are generated when a proton beam hits a device. Radiation that does not directly target the tumor is undesirable, especially

when treating pediatric patients, as they have an increased risk of developing neutron-induced secondary cancers later in life.[6]

Finally, because the devices are exposed to radiation during treatment, and become radioactive, they need to be stored for a period of time before they can be disposed of. The cost and space associated with storing these devices, and their environmental impact, must be considered when evaluating the delivery methods of proton therapy treatment.

DOSE SCULPTING AND EFFICIENCY

PBS delivers superior dose sculpting and higher beam efficiencies than other methods of proton beam delivery. This reduces unwanted side effects, improves long-term outcomes for patients, and improves the patient's quality of life.[7]

The method of proton beam delivery employed by PBS allows for a sharper Bragg peak than passive scattering – allowing for the treatment of deep-seated tumors. One of the biggest advantages of PBS is that each proton beam can be controlled in terms of position and intensity. The delivery of highly inhomogeneous treatment volumes is unique to PBS and allows for superior dose sculpting.[8]

Additionally, PBS can achieve beam efficiencies of close to 100%, while the beam efficiencies of passive scattering are typically between 3% and 15%.[9]

Due to the superior dose sculpting and high beam efficiencies, PBS delivers lower doses of radiation to critical structures and healthy tissue than other proton beam delivery methods. This reduces side effects and improves long-term outcomes for patients, and improves the patient's quality of life.[10,11]

PROTON THERAPY TREATMENT

To prepare for treatment, radiation specialists must determine location and shape of the target to determine the total number of protons to administer. By using either a computed tomography (CT) or magnetic resonance imaging (MRI) scan, radiation specialists calculate the depth protons must travel in order to determine the speed and shape of the beam.[12] This information allows for the development of a treatment plan.

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[9] H. Paganetti. *Proton Beam Therapy*. (IOP Publishing Ltd, 2017) doi: 10.1088/978-0-7503-1370-4
[10] H. Paganetti. *Proton Beam Therapy*. (IOP Publishing Ltd, 2017) doi: 10.1088/978-0-7503-1370-4
[11] P. Ahn, S. Sharma, O. Zhou, et al. A Comparative Quality of Life Cohort of Oropharyngeal Squamous Cell (OPSCC) Patients Treated With Volumetric Modulated Radiation Therapy (VMAT) Versus Proton Pencil Beam Scanning (PBS) *International Journal of Radiation Oncology • Biology • Physics*, 93(3), S71 (November 2015). doi: 10.1016/j.ijrobp.2015.07.171
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When treatment begins, before each treatment session, the patient receives either an x-ray or a CT to ensure that the patient is aligned in the correct position for highly-targeted dose delivery.

During most types of proton treatments, patients lay on a treatment table and a gantry delivers the proton beam at the angle specified in the treatment plan.

The number of treatment sessions a patient receives, and the length of each treatment session depends upon the type and stage of cancer or benign neoplasm.

A particle accelerator, most commonly a cyclotron or synchrotron, is used to raise protons to a high energy level. The protons are then isolated and accelerated up to 250 million electron volts. These highly-charged protons are directed by powerful magnets to a treatment room where radiation specialists use a beam delivery system to administer pre-calculated doses of radiation into the human body.

The team of medical professionals that participates in the preparation and administration of proton therapy treatment typically consists of a radiation oncologist, radiation physicist, dosimetrist, radiation therapist, and nurse. The radiation oncologist evaluates clinical patient information and determines appropriate therapy and dosing. In collaboration with the radiation oncologist, the remaining members of the team determine treatment administration procedures. A diagnostic radiologist will ensure precise imaging, while a radiation physicist and dosimetrist ensures accurate delivery of treatment through calculating exposure and dosing radiation. Radiation therapists perform the administration of treatments, and radiation therapy nurses work to manage any side effects of radiation treatment.

Proton therapy treatment is typically delivered in an outpatient setting. The treatment itself is painless and studies show that proton therapy treatment can lead to positive health outcomes for patients such as fewer short-term side effects, reduced risk of secondary malignant tumors, and faster recovery.[13,14,15]

ADVANTAGES OF PROTON THERAPY

Proton therapy's dosing method has had significant positive implications for the treatment of many types of cancers. One of the leading advantages of proton therapy is its precise level of dosing control. Due to the Bragg peak phenomenon, highly-charged protons form a more direct beam in route to treatment sites, compared to traditional forms of radiation therapy. This can result in an increased amount of radiation to the intended site and the elimination of a previously standard exit dose. In addition to improving the overall efficacy of treatment for many types of cancers, follow-up reports indicate fewer short-term side effects for patients and faster recovery times. Further, unlike traditional radiation methods, proton therapy may be indicated for some previously hard-to-treat cancers, like deep-seated tumors.

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[13] W.P. Levin, H. Kooy, J.S. Loeffler, T.F. DeLaney. Proton Beam Therapy. *Br J Cancer*. 93(8): 849–854 (October 2005). doi: 10.1038/sj.bjc.6602754

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BENEFITS TO USING PROTON THERAPY

The benefits to using proton therapy include:[16,17,18,19,20]

- Ability to target tumors with precision allowing treatment in close proximity to critical structures
- No exit dose, therefore, minimizing radiation exposure to healthy tissues and organs
- Ability to target tumors with high dose
- Fewer short-term side effects
- Reduces the risk of long-term side effects, including the development of secondary malignant tumors
- Faster recovery
- Cost savings due to shorter therapy duration and adverse effects avoidance

Precision of administration

Proton therapy offers the distinct ability to guide treatment beams within millimeters of a target. Providers can be more selective about areas requiring treatment and give higher doses of radiation. This is particularly beneficial for cases in which conventional radiotherapy dose limits on surrounding organs, such as the brain or spinal cord, must be established.[21] With greater accuracy in targeting, patients require fewer treatment sessions and experience fewer side effects.[22]

Minimal damage to surrounding healthy tissue and vital organs

As a highly-targeted treatment option, proton therapy can help patients avoid the effects of traditional photon therapy such as hearing and vision loss, heart disease, and radiation burns.[23] In children, whose organs and bones are still developing, leaving surrounding tissue unexposed to radiation can stave off future growth problems. When tumors are located near vital organs, precise radiation beams give providers a more efficient and direct way to treat unhealthy cells.[24]

Fewer side effects than photon therapy

Proton therapy is non-invasive and painless. It reduces the incidence and severity of side effects associated with traditional photon therapy.[25] Many patients report maintaining the

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[22] E.B. Holliday, A.S. Garden, D.I. Rosenthal, et. al. Proton Therapy Reduces Treatment-Related Toxicities for Patients with Nasopharyngeal Cancer: A Case-Match Control Study of Intensity-Modulated Proton Therapy and Intensity-Modulated Photon Therapy. *International Journal of Particle Therapy*,2(1), 19-28 (2015). doi:10.14338/ijpt-15-00011.1
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quality of life they had pre-diagnosis – continuing at their jobs, going to the gym, and enjoying time with family.[26] With lower treatment exposure to healthy tissue, the likelihood decreases that secondary malignancies will develop as a result of unnecessary radiation exposure.[27]

Cost savings due to shorter therapy duration and adverse effects avoidance

Proton therapy can be used to deliver higher doses of radiation, and the therapy's ability to leave surrounding tissue undisturbed, are key factors in cost savings for both short- and long-term care costs.[28] Often times patients require fewer treatments with proton therapy than with traditional X-ray therapy, and many patients can receive proton therapy treatment in an outpatient setting. The ability to couple proton therapy with other treatments, such as chemotherapy, also increases the likelihood that cancers can be eradicated with greater efficiency.

WHO CAN BENEFIT FROM PROTON THERAPY?

Patients with tumors that are in close proximity to vital organs, critical structures, or significant normal tissue may benefit most from proton therapy.[29] The precision with which the treatment can be administered makes proton therapy ideal for treating tumors near or in the brain, head and neck, spinal cord, breast, prostate, and lung. Pinpoint accuracy means that treatment doses can be designed to deposit less radiation into healthy tissues around these sensitive sites. Additionally, radiation oncologists do not have to account for the need of an exit dose, as protons act in accordance with the Bragg peak phenomenon – their energy peaking before immediately coming to rest within the targeted site. Finally, with precision targeting, and without the consideration of an exit dose, patients are able to tolerate an increased dose of radiation – leading to fewer overall treatment sessions.

Pediatric patients also benefit significantly from proton therapy. Their growing and developing bodies can endure harmful side effects from traditional forms of radiation therapy. Proton therapy represents an opportunity for providers to more safely administer treatment to children without disrupting growth hormone receptors or damaging adjacent bone or soft tissues. Further, proton therapy has been shown to improve long-term health outcomes in pediatric patients as it reduces the risk of later-life secondary cancers.[30,31]

As ongoing clinical research continues to grow and support the efficacy of proton therapy, more and more medical facilities are choosing to make it available to their providers and patients.

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CLINICAL APPLICATIONS

Proton therapy is most often used in pediatric cancer cases and in adults who have well-defined tumors in or near organs such as the brain, prostate, head, neck, bladder, lungs, or the spine. It is also used to treat tumors for which complete removal cannot be achieved by surgery.[32] The treatment of these conditions, as well as the treatment of childhood cancers, benefits significantly from the increased dosing and precision administration of proton therapies.[33]

Radiation treatment of non-cancerous conditions affecting vital organs and tissue, such as acoustic neuromas and other benign tumors, has traditionally carried a risk of damaging surrounding healthy cells, leading to unwanted side effects. Defects of the circulatory system, such as arteriovenous malformations, as well as endocrine conditions like pituitary adenomas, present challenges to practitioners due to the small size of the affected area.[34] With proton therapy's precise beam, treatment of conditions that could have once impaired hearing or vision can now be treated with a lower risk of these significant side effects.

The prescribed use of proton therapy continues to expand as short- and long-term studies confirm its effectiveness and efficacy. Researchers are currently studying proton therapy's use in the treatment of many more cancers, including liver, brain, and pancreatic cancers, as well as soft tissue sarcomas. As more research emerges, the therapy is well-positioned to be a primary radiotherapy modality for many cancers and non-cancerous conditions.

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Collaboration fuels innovation. We have long-standing partnerships with the Massachusetts Institute of Technology, Bates Research and Engineering Center, Massachusetts General Hospital.

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