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Proton therapy for cancer treatment

Devanshi Dinesh Mayani
Sinhgad Institute of Pharmaceutical Sciences, Department of Pharmacy, 54/G/1 Gaurakshak Building, 1st Fanaswadi, Thakurdwar, Mumbai 400002, India

Abstract
Proton beam therapy is the latest advancement in the treatment of various types of cancer. It is a precise form of radiotherapy. It uses a beam of protons to target the cancer cells and destroys them. It scores high on precision and effectiveness when compared to other conventional cancer treatments like surgery, chemotherapy and xray radiotherapy. Proton beam therapy destroys the cancerous cells without harming the healthy cells. Thus it considerably reduces the side-effects that accompany conventional cancer treatments. Supporters say the technology allows physicians to treat a broad spectrum of cancers with few adverse effects, while more precisely targeting tumor cells with higher doses of radiation. Detractors say proton beam therapy is hugely expensive and has not been shown to be superior to conventional radiation treatment. With proton beam therapy, physicians use a cyclotron to accelerate protons and fire them directly into tumor cells with submillimeter precision. Because healthy tissue is largely spared, oncologists can, in theory, deliver much higher doses of radiation, while improving local control and reducing the risk for recurrence and morbidities.

Keywords
cancer, proton therapy, oncology

Proton therapy for cancer treatment

Proton therapy is a type of external beam radiotherapy. It works by aiming energetic ionizing particles (in this case, protons accelerated with a particle accelerator) onto the target tumor.[1,2] These particles damage the DNA of cells, ultimately causing their death. Cancerous cells, because of their high rate of division and their reduced ability to repair damaged DNA, are particularly vulnerable to attack on their DNA.

Due to their relatively large mass, protons do not scatter much in the tissue; the beam does not broaden much and stays focused on the tumor shape without much damage to the surrounding tissue. All protons of a given energy have a certain range; no proton penetrates beyond that distance.

Furthermore, the dose delivered to the tissue is maximum just over the last few millimeters of the particle's range; this maximum is called the Bragg peak.[3] This depth depends on the energy to which the particles were accelerated by the proton accelerator, which can be adjusted to the maximum rating of the accelerator (typically 70–250 MeV). It is, therefore, possible to focus the cell damage due to the proton beam penetrating deep into the tissues where the tumor is situated; tissues situated before the Bragg peak receive only a reduced dose, while the ones situated after the peak receive none.[4]

History

- It dates back to 1946 when Wilson advocated proton utilization for medical science and Tobias and other researchers treated hypophysis tumor by proton beams at the Lawrence Berkeley National Laboratory of University of California.
- Proton therapy was started at the Uppsala University in Sweden and Massachusetts General Hospital (MGH) of Harvard University in the USA. Also in Japan, the National Institute of Radiological Sciences started clinical studies with 70-MeV cyclotron in 1979, and the University of Tsukuba started proton cancer therapy with booster accelerator, a high-energy accelerator, for liver cancer, esophagus cancer, lung cancer, and brain tumor as its object diseases.

Corresponding author:
Devanshi Dinesh Mayani, Sinhgad Institute of Pharmaceutical Sciences, Department of Pharmacy 54/G/1 Gaurakshak Building, 1st Fanaswadi, Thakurdwar, Mumbai 400002, India
Email: dmayani89@gmail.com

- The first suggestion that energetic protons could be an effective treatment method was made by Robert R. Wilson in a paper published in 1946 while he was involved in the design of the Harvard Cyclotron Laboratory (HCL).
- The first treatments were performed at particle accelerators built for physics research, notably the Berkeley Radiation Laboratory in 1954 and at Uppsala in Sweden in 1957.
- In 1961, a collaboration began between HCL and MGH to pursue proton therapy.
- Over the next 41 years, this program refined and expanded these techniques while treating 9116 patients before the cyclotron was shut down in 2002.
- Following this pioneering work, the first hospital-based proton treatment center of the world was built in 1990 at the Loma Linda University Medical Center (LLUMC) in Loma Linda, California (recently renamed the James M. Slater Proton Therapy Center), where more than 13,000 patients with 50 different types of tumor have been treated so far (end of 2008).[5]
- The Northeast Proton Therapy Center at MGH (recently renamed the Francis H. Burr Proton Therapy Center), to which the HCL treatment program was transferred during 2001 and 2002.
- The first proton therapy center in western Europe has been in operation at the Paul Scherrer Institute (PSI) in Villigen, Switzerland, since 1984.

Comparison with surgery

- Application of radiation is statistical in nature. This is because the cure rate of radiation therapy is based on the probability of cell kill within a geometric margin. The only way to 'know' if radiation is successful is if a cell does not multiply.
- The decision to use surgery or proton therapy (or in fact any radiation therapy) is based on the tumor type, stage, and location.
- In some instances surgery is superior (e.g., cutaneous melanoma), in some radiation is superior (e.g., skull base chondrosarcoma), and in some they are comparable (e.g., prostate cancer).[6,7]

Comparison with conventional X-ray radiotherapy

The proton treatment method is of interest because when applied correctly, it can accurately target and kill tumors, both near the surface and deep seated within the body, while minimizing damage to tissue distal from the point of entry, that is, protons stop.[2] For this reason, it is favored for treating certain kinds of tumors where conventional X-ray radiotherapy would damage the surrounding radiosensitive tissues to an unacceptable level.[2] This is of particular importance in the case of pediatric patients where long-term side-effects, such as residual occurrence of secondary tumors resulting from the overall radiation dose to the body, are of great concern. Because of the lower dose to healthy tissue protons have less severe side-effects than conventional radiation therapy.[8]

One area where proton therapy has had a considerable success is in treating choroidal malignant melanomas, a type of eye cancer for which the only known treatment was enucleation (removal of the eye[9]).

Methodology of proton therapy

There is a significant difference between standard (X-ray) radiation treatment and proton therapy. If given in sufficient doses, X-ray radiation techniques will control many cancers. But, because of the physician's inability to adequately conform the irradiation pattern to the cancer, healthy tissues may receive a similar dose and can be damaged. Consequently, a less-than-desired dose is frequently used to reduce the damage to healthy tissues and avoid unwanted side-effects. The power of protons is that higher doses of radiation can be used to control and manage cancer while significantly reducing damage to healthy tissue and vital organs.[10] Essentially, protons are a superior form of radiation therapy. Fundamentally, all tissues are made up of molecules with atoms as their building blocks. In the center of every atom is the nucleus. Orbiting the nucleus of the atom are negatively charged electrons.[11]

When energized charged particles, such as protons or other forms of radiation, pass near the orbiting electrons, the positive charge of the protons attracts the negatively charged electrons, pulling them out of their orbits. This is called ionization; it changes the characteristics of the atom and consequentially the character of the molecule within which the atom resides. This crucial change is the basis for the beneficial aspects of all forms of radiation therapy.[12] Because of ionization, the radiation damages the molecules within the cells, especially the DNA or genetic material. Damaging the DNA destroys specific cell functions, particularly the ability to divide or proliferate. Enzymes develop with the cells and attempt to rebuild the injured areas of the DNA; however, if damage from the radiation is too extensive, the enzymes fail to adequately repair the injury. While both normal and cancerous cells go through this repair process, the ability of a cancer cell to repair molecular injury is frequently inferior.[13] As a result, cancer cells sustain more permanent damage and subsequent cell death than the normal cell population. This permits selective destruction of bad cells growing among good cells.[9]

Both standard X-ray therapy and proton beams work on the principle of selective cell destruction.

The major advantage of proton treatment over conventional radiation, however, is that the energy distribution of protons can be directed and deposited in tissue volumes designated by the physicians in a three-dimensional (3D) pattern from each beam used.[14] This capability provides greater control and precision and therefore superior management of treatment. Radiation therapy requires that conventional X-rays be delivered into the body in total doses sufficient to assure that enough ionization events occur to damage all the cancer cells.[15] The conventional X-rays lack of charge and mass, however, results in most of their energy from a single conventional X-ray beam being deposited in normal tissues near the body's surface, as well as undesirable energy deposition beyond the cancer site. This undesirable pattern of energy placement can result in unnecessary damage to healthy tissues, often preventing physicians from using sufficient radiation to control the cancer.[16]

Protons, on the other hand, are energized to specific velocities. These energies determine how deeply in the body the protons deposit their maximum energy. As the protons move through the body, they slow down, causing increased interaction with the orbiting electrons.[17]

Maximum interaction with electrons occurs as the protons approach their targeted stopping point. Thus, maximum energy is released within the designated cancer volume. The surrounding healthy cells receive significantly less injury than the cells in the designated volume.[18]

As a result of protons' dose distribution characteristics, the radiation oncologist can increase the dose to the tumor while reducing the dose to the surrounding normal tissues. This allows the dose to be increased beyond that which less-conformal radiation will allow. The overall effects lead to the potential for fewer harmful side-effects, more direct impact on the tumor, and increased tumor control.[19]

The patient feels nothing during the treatment. The minimized normal-tissue injury results in the potential for fewer effects following treatment, such as nausea, vomiting, or diarrhea. The patients experience a better quality of life during and after proton treatment.[20]

Irradiation method and technique

Proton therapy requires very critical therapy planning. Therefore, advanced techniques which make a clear distinction from conventional radiotherapies have been adopted and are also under development.

The following irradiation techniques are now under development or already in use.

1. Patch field irradiation: This is a useful method for the case involving a large lesion or the lesion adjoining important organs, and a technique to split the irradiation range into some ranges, or to irradiate from various directions.[21]
2. Breathing synchronous irradiation: This is a technique to irradiate in synchronization with a portion of the breathing phase, the case if the irradiated organ moves by breathing, like lung and liver.[22]
3. High-precision positioning device: This is a technique to precisely position the target by using fixation devices to lessen shifting error by body displacement, CT, and MRI.[23]
4. High-precision 3D dose distribution calculating system: This is a system to plan the 3D dose distribution appropriately and efficiently based on the image data obtained by CT and MRI. It is necessary to make a plan for delivering enough doses to the target and minimizing it to the surrounding important organs.[24]
5. Spot scanning: This is a technique to scan the target in its shape with beams. It delivers enough doses to the target by changing the energy of proton beams and also the depth of the magnified Bragg peak in series. We at WERC are working on researches for advancing proton therapy.[25–27]

Cancers treated by proton therapy

Proton therapy goes to a specific area of the patient's body. So, this therapy can best shrink tumors that have not spread to other parts of the body and are located in one area, especially a tumor next to critically important tissues (such as the optic nerves that travel between the eye and brain) that need protection from radiation damage.[28]

Proton therapy is useful for treating cancer in children because it lessens the chance of harming healthy, developing tissue.[3,30] Children may receive proton therapy for cancers of the central nervous system (brain and spinal cord) and the eye, such as retinoblastoma and orbital rhabdomyosarcoma.[29]

Some.

Compared with standard radiation treatment, proton therapy has several benefits, including:

- Reduces the risk of radiation damage to healthy tissues.
- May allow a higher radiation dose to be directed at some types of tumors, which may keep the tumor from growing or spreading.[10]
- May result in fewer and less severe side-effects (such as low blood counts, fatigue, and nausea) during and after treatment.[31,32]

Pediatric proton therapy

The treatment of childhood tumors is an area where proton therapy may significantly reduce the acute and

long-term complications associated with conventional radiation therapy.[33] Pediatric cancer treatment has significantly improved over the past few decades and now the 5-year overall survival is approximately 80%. There are approximately 270,000 survivors of childhood cancers in the USA alone.[34] However, the pediatric population is exquisitely sensitive to the effects of radiation therapy. In this group of patients, cure is not enough. Long-term sequelae including growth abnormalities, second malignancies, neurologic complications, reduced IQ, cardiac and pulmonary toxicities, and infertility may all be reduced with the use of proton therapy. Up to two-third of the patients will develop long-term toxicity, some of which will be fatal. These toxicities can cause a great deal of emotional and financial stress for the patient. It is known that age at the time of radiation as well as the dose to which the child was treated are important risk factors. Specifically, developing tissues are more sensitive to radiation, and hence, there can be detrimental effects even at low doses. With improved outcomes, there is a greater concern regarding treatment-induced cancers as there are a greater number of potential years of life during which the secondary malignancy can manifest. Technical improvements have focused on decreasing toxicity while maintaining good outcomes.[35] Numerous clinical trials have attempted to eliminate radiation; however, radiation still plays an important role in more than half of pediatric patients. While intensity-modulated radiation therapy (IMRT) can deliver dose with a greater conformity, it does bathe a significant amount of normal tissues with low doses of radiation, which can be significant in younger patients.[36]

Proton therapy can reduce the integral radiation dose by two- to-threefold compared with any type of photon-based therapy. It is proposed that, due to the decreased normal tissue dose, proton treatment will lead to the development of less secondary malignancies.[37]

Issues at hand

1. Proton beam therapy is generally considered superior to X-rays when treating pediatric and head and neck cancers, but there is debate about the appropriateness of its use in treating other cancers. More evidence from clinical trials is needed to determine whether the treatment improves survival and decreases late effects compared with conventional radiotherapy.
2. Proton beam clinics are expensive and studies indicate that they may not be worth the cost. Proponents argue that all new technologies are expensive initially, but the costs will come down as more centers come online. They argue that reduced spending to treat toxicities and recurrence will make proton beam therapy more cost effective over time.
3. Proton beam therapy is likely to have the most effect on pediatric oncology. Because the therapy exposes only a small amount of normal tissue to radiation, oncologists hope that proton beam therapy will spare survivors of childhood cancers from years of late effects and lowered quality of therapy.

Present proton therapy centers

1. In the UK, it is currently only available at the Clatterbridge Centre for Oncology in Bebington on the Wirral, Merseyside.
2. In China, the only proton therapy machine is located in the Wanjie Proton Therapy Center in Zibo, Shandong.
3. In the USA, it is available in Sacramento, CA, at the University of California, Davis, and the UC Davis Proton Facility, which is operated exclusively by the UC San Francisco Department of Radiation Oncology.
4. Since 2004, the Midwest Proton Radiotherapy Institute at Indiana University and in 2006, the University of Texas, MD Anderson Cancer Center in Houston, TX, and The Institute in Jacksonville, FL.[16]

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