The promise of proton therapy

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An estimated 60% of all cancer patients undergo some sort of radiation therapy during their course of treatment,[1] and despite advances in radiation therapy technology, many suffer from side effects caused by conventional photon-based (x-ray) radiation therapy.

There is, however, a silver lining. As an alternative to conventional treatments, patients increasingly have access to proton radiation therapy. With proton therapy, the majority of radiation energy from a proton beam is actually deposited in the targeted cancer,[2] causing less damage to healthy tissue compared with other radiation alternatives, and resulting in fewer short- and long-term side effects.[3-9]

"What protons allow you to do is deliver the same type of treatment of x-ray therapy while sparing more normal tissue than with x-ray therapy," explained Dr. Carl Rossi, Medical Director of Scripps Proton Therapy Center, San Diego, CA.

While proton therapy has been used clinically for more than 2 decades, the high cost of the technology has limited access to the treatment. That is changing, however, as manufacturers develop more compact systems and cost-effective models, which lower the initial investment, enabling hospitals to offer a new life saving treatment, often resulting in a better quality of life.

The proton advantage

The unique dose distribution of protons and spread-out Bragg peak enable the delivery of highly conformal radiation to cancers located adjacent to critical normal structures without damaging healthy surrounding tissue.[2] This reduces the negative side effects of treatment and helps sustain patient quality of life.

"The advantage of proton therapy is that proton particles have mass, and you can control the depth of penetration better, as opposed to an x-ray that passes through the patient's body. Protons deliver the radiation to the tumor, and then the proton beam stops, so that there is not excess radiation delivered beyond the tumor," explained Henry Tsai, MD, a radiation oncologist at The ProCure Proton Therapy Center in Somerset, NJ.

This can result in sparing 60% to 80% of the healthy surrounding tissue, indicated Brian Chon, MD, Medical Director, The ProCure Proton Therapy Center of New Jersey. "Sparing healthy tissue and organs helps reduce the impact of side effects common in traditional photon therapy and allows for treatment in difficult locations of the body," said Dr. Chon.

The price of progress

Despite the clinical benefits of proton therapy, broad adoption of the technique has been greatly limited by the enormous cost, which can run into the $100 millions. In addition, there is the high cost of the large footprint and the technical complexity of traditional proton therapy systems.

A recent study by KLAS, an independent research firm, found that concerns about market saturation and an estimated initial investment of $150 to $200 million would likely deter investors from healthcare facilities in proton therapy over the next 5 years.[10,11] In addition to cost, survey participants also indicated they had reservations about return on investment due to the patient referral base, staffing requirements, and ongoing maintenance costs.

These factors contribute to the fact that over several decades just 2 large institutions in the United States—Loma Linda University Medical Center in Los Angeles, CA, and Boston's Massachusetts General Hospital (MGH)—have had the patient volume and funding to feasibly offer proton therapy. These traditional centers have 200-ton to 250-ton cyclotrons, requiring a very large infrastructure for treatment rooms.

However, with recent developments in proton therapy technology, cyclotrons have smaller footprints and run just a fraction of the cost of full-sized systems, thus changing the landscape from a $150 million investment to a $25 million solution.

"The technology has gone from something that had to be built in a national

FIGURE 1. Varian Probeam treatment room. Scripps Proton Therapy Center is being developed by Advanced Particle Therapy, LLC of San Diego, CA, and will be operated by Scripps Health and Scripps Clinic Medical Group. The center is due to open for patient care in summer 2013.

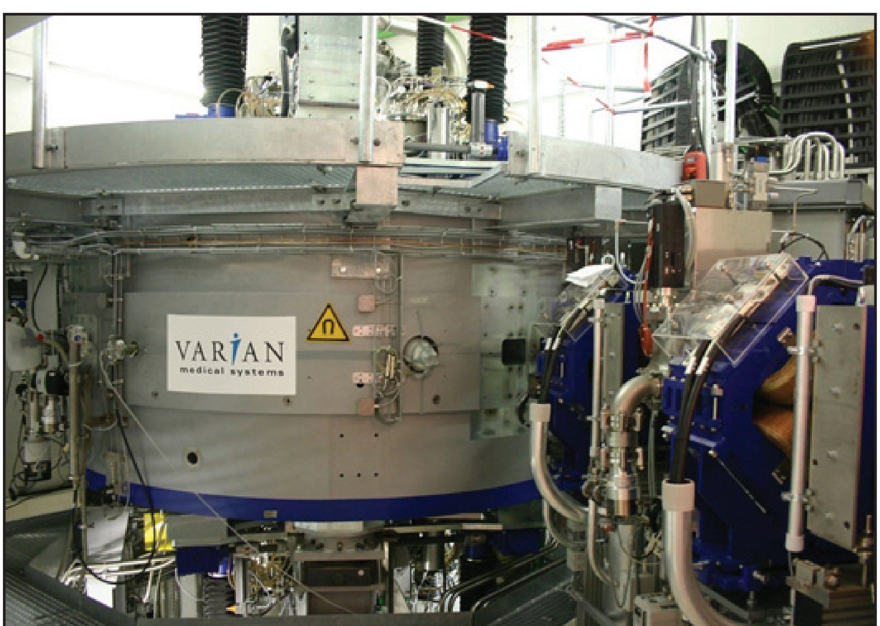

FIGURE 2. Cyclotron Varian ProBeam. A 90-ton cyclotron (left) is the centerpiece of the fully integrated ProBeam proton therapy system at Scripps Proton Therapy Center. The technology is manufactured by Varian Medical Systems. (Photo courtesy of Varian Medical Systems).

laboratory to something you can now buy. Today, there are a number of vendors you can chose from, and there is competition in the market, including Varian, Hitachi, IBA, and Mevion," said Dr. Rossi. "Facilities are now designed for a high-patient throughput. At our facility, with 5 treatment rooms, we expect to treat up to 200 patients a day—this allows us to spread the unit cost per treatment. We are now running a 16-hour treatment day. That's helping reduce the costs."

Currently, Scripps Proton Therapy Center is being developed by Advanced Particle Therapy, LLC of San Diego, CA, and will be operated by Scripps Health and Scripps Clinic Medical Group. The center is due to open for patient care in summer 2013. Scripps is installing Varian's ProBeam system and will offer active beam scanning, also called pencil-beam scanning or intensity-modulated proton therapy (IMPT). With IMPT the beam conforms more closely to the tumor, better sparing surrounding healthy tissue from harm.

In 2013, ProBeam is due for an additional upgrade with cone-beam computed tomography (CT) imaging. While 3-dimensional (3D) imaging is common in linear accelerators and used intensively for stereotactic radiosurgery, the standard for proton therapy is 2-dimensional (2D) stereotactic imaging. Cone-beam CT will allow for volumetric imaging, producing 3D image sets, and therefore enable radiosurgery with the cone-beam CT on the ProBeam system.

The Mayo Clinic is scheduled to treat its first patient with proton therapy at it's Rochester, MN-site in the summer of 2015 and at its Arizona location in 2016—all 8 treatment rooms will be operational by 2017. The Mayo Clinic Proton Beam Therapy Program will exclusively feature IMPT and is working with Hitachi Medical Systems America to implement a synchrotron.

TECHNOLOGY TRENDS

IBA-Philips Proton Therapy. IBA Group partnered with Philips Healthcare to install the Philips Ambient Experience at Willis-Knighton Cancer Center in Shreveport, LA. The room is designed to promote patient relaxation during proton treatments.

"[The Hitachi system] is a much smaller and less expensive version of what was used in the past. So the building does not need to be as large, and it is less costly to operate because there are fewer parts," explained Robert L. Foote, MD, Mayo Clinic's Chairman of Radiation Oncology. "We wanted to have the most state-of-art technology available when we started treating patients, and we thought that would be the intensity-modulated protons, not the scattered protons everyone is using now, and Hitachi had an FDA-approved intensity-modulated proton option available that was in use at MD Anderson Cancer Center. Our physicists worked with Hitachi to design a smaller, less expensive synchrotron, gantry, and robotic patient positioning system to reduce the cost of the equipment and the footprint of the building."

Designed to provide a turnkey solution, the model for ProCure Proton Therapy Centers (ProCure) is designed to cost-effectively open and manage proton therapy centers. Procure opened the first center in Oklahoma City, in July 2009, and in 2012 celebrated the inauguration of its tenth location in Somerset, NJ. The new site has 4 treatment rooms equipped with the IBA Proton Therapy System manufactured by IBA, SA (Belgium).

"While traditional centers have 200- to 250-ton cyclotrons, requiring a very large infrastructure for treatment rooms, the cyclotrons have a smaller footprint," explained Dr. Chon. The smaller footprint lowers the overall size and cost of the installation.

One of the leaders in proton therapy system technology is Ion Beam Applications SA (IBA) of Belgium, which has installments at MGH, University of Pittsburgh Medical Center (UPMC), in addition to the ProCure Proton Therapy Center of New Jersey. In 2009, IBA introduced a smaller and more economical 2-room treatment solution called Proteus Nano. Just one year later, the company rolled out an even more cost-effictive solution, Proteus One, a single-room system one-third the size of the current gantry configuration and which offers a smaller cyclotron, a shorter proton-beam route from the cyclotron to the treatment room, and a more compact gantry. Proteus ONE's smaller treatment room is designed to reduce costs, minimize space, and shorten the installation time required to build a proton therapy center. In addition, the Proteus ONE supports pencil beam scanning proton delivery, or IMPT, and has integrated 3D cone-beam CT imaging that rotates around a patient, capturing detailed tumor images.

Another way IBA is pioneering innovation in proton therapy treatment is by creating a more comfortable environment for patients. IBA Group and Royal Philips Electronics have teamed up to build a state-of-the-art, patient-centered proton therapy treatment room. A new addition to the Willis-Knighton Cancer Center in Shreveport, LA, will house the first IBA installation to incorporate the Philips Ambient Experience. The Philips Ambient Experience promotes patient relaxation during proton treatments by permitting patients to selectively add comforting light, sound, and images to the treatment room environment before they begin therapy. The ambience is designed to transform the patient and staff experience into one that is comforting and reassuring. The $40 million project at Willis-Knighton marks the first center to utilize IBA's Proteus ONE, and is expected to begin treating cancer patients with protons in early 2014.

As manufacturers embrace the concept that less is more, another compact model is the MEVION S250 proton therapy system, a single-vault unit by Mevion Medical Systems that recently received FDA 510(k) clearance. The system's accelerator has a diameter of just 6 feet (1.8 m), which has a smaller footprint than most other systems. The first MEVION S250 installation will be completed at the Kling Center for Proton Therapy at Barnes Jewish Hospital at Washington University in St. Louis, MO, and Mevion will be delivering and installing more than a dozen MEVION S250 proton therapy systems worldwide within the next 2 years.

Another turnkey solution is available with the Conforma 3000 by Optivus, which provides an efficient modular design. The system evolved out of the technology used at the Loma Linda University Medical Center. With the Conforma 3000, facilities can be configured with 1 to 5 gantries using a variety of floor plans that can be developed to work with most existing facilities.

Quality-of-life

One of the biggest value propositions for proton therapy is that it minimizes side effects and morbidity, resulting in a better quality of life for patients compared to photon radiation therapy.

"The number one advantage of proton therapy is it is a safer treatment with fewer short-term and long-term complications, particularly in the pediatric and young adult population," indicated Robert Foote, MD, Mayo Clinic's Chairman of Radiation Oncology.

There is growing evidence that proton therapy results in a better quality-of-life for patients. In a recent study, investigators at MGH and UPMC evaluated patients fighting prostate cancer. They found those treated with proton beam therapy were likely to experience a better quality-of-life than those treated with traditional radiation therapy.

In a nonrandomized study,[12] researchers opened a comparison of proton beam therapy (PBT) and intensity-modulated radiation therapy (IMRT) for patients with localized prostate cancer. They evaluated the side effects of PBT, 3D conformal radiation therapy (3D CRT), and IMRT. They found patients undergoing PBT treatment had a higher quality-of-life in early follow-up and at 2 years, compared 3D CRT and IMRT.

Proton vs. Photon Therapy

Despite growing evidence that quality-of-life is better with proton therapy, there is an ongoing debate as to whether the difference between proton therapy and photon or x-ray based radiation therapy treatment is clinically significant.

"What people argue about is whether that difference in dose is clinically relevant. My counter to that is there is no unimportant radiation dose, if there's a way to not treat that normal tissue, you should pursue it," said Dr. Rossi.

The primary advantages of proton therapy, says Dr. Rossi, is it causes less damage to healthy surrounding tissue than photon therapy dose and it gives greater control over the radiation beam to better contour dose to the target.

"If you are talking about radiation dose to normal tissue, proton therapy is superior in virtually any situation you can think of. If you have a very small 2-cm or 3-cm field, there may not be that much of a difference. Beyond that, the larger the field you have to treat, the more irregularly shaped, the greater the disparity in normal tissue radiation dose between proton and IMRT," said Dr. Rossi.

Ultimately, said Dr. Rossi, "The main reason for offering proton therapy is that, irrespective of the type of x-ray therapy (XRT), you can do everything with proton that you can do with XRT, such as intensity-modulation and stereotactic, but you are using a radiation beam that stops. You can use the same type of set up with image-guidance like you use for high-precision x-ray therapy, but because you are using a beam that stops you treat far less normal tissue than you do with x-ray."

Nonetheless, the debate between proton therapy versus conventional radiation therapy continues. The authors of the study evaluating the side effects of PBT, 3D CRT, and IMRT[12] recognize the need for a randomized control trial. In fact, MGH and UPMC have partnered to launch a trial randomizing low- and intermediate-risk prostate cancer patients to IMRT vs. proton beam radiation to evaluate quality-of-life outcomes, cost-effectiveness, and physics and radiobiology endpoints.[12]

Increased control, less toxicity

From the patient's perspective, quality-of-life is second in importance to nonrecurrence in cancer. The increased control and lower toxicity of the proton beam may allow a larger amount of dose to be delivered per fraction, and therefore may prove more effective.

"In some instances, we can deliver more dose. In the brain or spine, where you want to deliver more radiation, there is a significant advantage with proton therapy, and it still delivers less radiation to surrounding tissues," Robert Foote, MD, Mayo Clinic's Chairman of Radiation Oncology.

Proton therapy is especially promising for treating organs affected by motion and near to other critical organs, including the prostate, which is adjacent to the rectum and bladder. A recent study on proton therapy demonstrated extremely low rates of grade > 3 GU and GI toxicities and extremely high disease control, presumably related to improved radiation dose distributions over what can be achieved with IMRT.[12] The low toxicity of proton therapy makes it particularly appropriate for pediatric patients, whose growing bodies are more sensitive to radiation.

Other clinical applications highly indicated for proton therapy include anatomical areas with highly sensitive surrounding structures, such as the brain and spine. Proton therapy, for example, effectively treats chondrosarcomas or chordomas involving the base of the skull or the spinal axis; as cranial nerves are located at the base of the skull, the optic nerves are close by, as well as the optic chiasm.

"In the brain or spine, where you want to deliver more radiation, there is a significant advantage with proton therapy, and it still delivers less radiation to surrounding tissues," indicated Dr. Chon. "Proton therapy can spare 60% to 80% of the healthy surrounding tissue. That is why we are treating pediatric

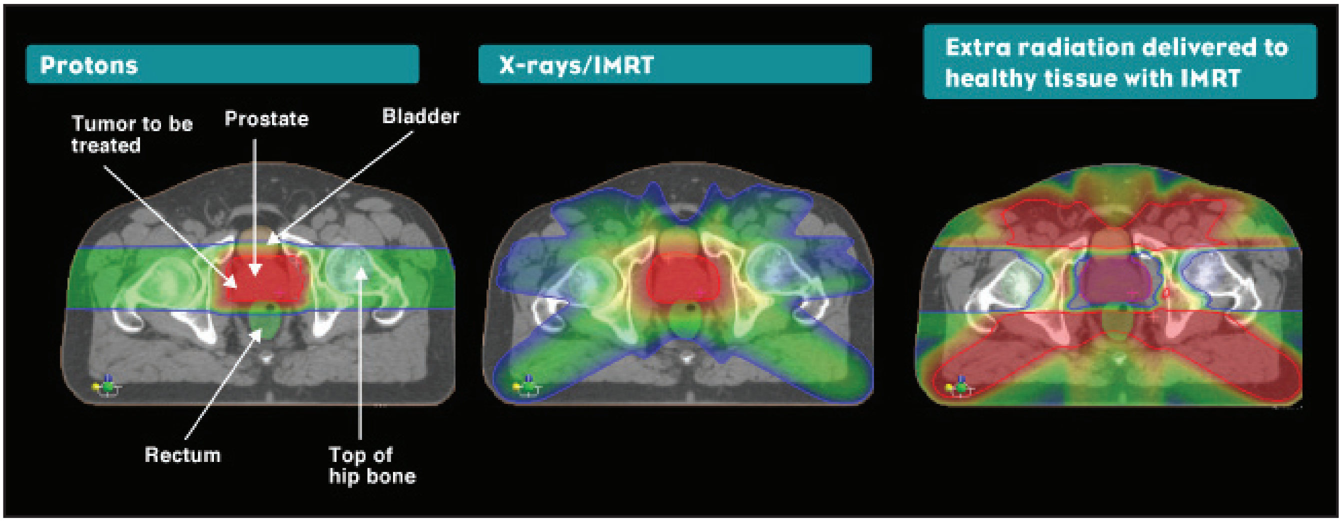

FIGURE 3. Proton therapy achieves better conformation to the tumor and minimizes the dose to healthy tissue. Source: ProCure Training and Development Center

patients who clearly benefit from it. We are also treating patients with tumors of the skull, brain, and spinal chord, and are working on expanding proton therapy into the lung and abdomen."

Next-generation proton technique

While adoption of proton therapy is just beginning to blossom, the technology is already on to the next-generation proton therapy technique—IMPT.

Mayo Clinic, for example, has decided to use IMPT as opposed to scatter-beam therapy. Although Dr. Foote acknowledges there have not been phase III controlled clinical trials demonstrating the superiority of IMPT over scatter-beam technology in terms of safety or efficacy, Dr. Foote and his clinical team have observed the technique at MD Anderson in Texas and Paul Scherrer Institute in Switzerland where they have been using IMPT for many years. At those prestigious institutions, Dr. Foote explains, "they have found that IMPT compared to scatter-beam therapy seems to be as effective using typical doses to tumors, while reducing dose to normal organs and tissues."

"The scattered beam conforms very tightly to the distal edge of the tumor, but that creates some hot spots on the proximal end of the tumor and out into the normal tissue. With the intensity-modulated protons, we'll be using pencil-beam scanning, so a pencil-sized beam will put small "dots" of radiation energy within the tumor and magnets will scan the beam back and forth, painting dose within the tumor," he said. In summary, "The pencil-beam scanning is more targeted and precise, and you get rid of the expense of collimators and compensators. It is also more efficient for a higher throughput of patients," added Dr. Foote.

Dr. Rossi believes IMPT is the next generation of proton therapy treatment. "With an actively scanned beam, as compared to a scatter beam, I can spare far more normal tissue, and secondly, with an active-scan beam, I am now able to treat much larger treatment fields than I could in the past. Previously, our maximum beam size was 17 cm, that's fine for treating small structures like the prostate or brain tumors, but what if you have to treat someone's pelvis because they have lymph nodes involved, or what if you have to treat the pelvis or mediastinum in lungs. The probing system allows you to a treat a 40-cm x 30-cm field, the same size as you can treat on a linear accelerator," said Dr. Rossi.

Growing patient populations

While there are concerns surrounding sufficient volumes of patients seeking proton therapy, the leading centers do not foresee a shortage of patients in the coming years.

At Mayo Clinic, they expect to treat an estimated 1,240 patients per year in Rochester, and another 1,240 patients per year at their facility in Phoenix. The patient population will consist of pediatrics, adolescents, and young adults with cancers, such as brain tumors, rhabdomyosarcomas, and lymphomas. Mayo Clinic has an active and growing practice for ocular melanomas and a neurosurgery group doing skull-base and spine surgery for chordomas and chondrosarcomas. For certain types of cancer, they will treat lung, breast, and a variety of gastrointestinal cancers, such as esophageal, gastric, and hepato-biliary tumors. There will be some selected prostate cancers with high PSA, high Gleason score, and advanced T-stage treated with hypofractionation.

Dr. Foote noted, "We will be participating in clinical trials for prostate cancer using just 5 treatments rather than the 40 or more treatments. We are currently reimbursed per treatment, so the best way to reduce the cost for proton beam therapy is to reduce the number of treatments. If we can safely reduce the number of treatments from 44 to 5, that will be in the best interest of the patient and the insurer."

He added, "The goal is to have everyone treated on a clinical trial so that we can document lowering of acute toxicity, and lowering of late complications as well as lowering overall costs associated with treating the cancer."

Cutting cost through better outcomes

As the technology evolves, the cost gap between x-rays and protons continues to narrow. In addition, reduced side-effects for patients impact their quality-of-life, likelihood of recurrence, and the overall cost to the healthcare system. While the initial cost of treatment with protons is higher than that of photon therapy, reduced side-effects results in an overall cost savings over a lifetime.

The cost of side-effects is well illustrated over the lifetime of a pediatric patient. Side effects of photon therapy include hypothyroidism and growth hormone deficiency, seizure disorders, and auditory and visual impairment after treatment have also been reported.[13,14] One study of children with medulloblastoma treated with X-rays estimated the risk of hearing loss at 13% because of radiation to the inner ear.[13] The risk of secondary cancers further adds to the cost of patient care. In one study where researchers assessed the potential influence of dose distribution on the incidence of secondary cancers in a pediatric patient with medulloblastoma, they estimated that the rate of secondary tumors would be 8 times lower with proton therapy than with IMRT (X-ray) treatment (0.05% vs 0.43%).[15]

"It is true that the initial cost with proton therapy is more than x-rays, but when you follow the young child throughout the course of their lifetime and find that their IQs are higher with protons, they don't need hearing aids as often, they don't need special education as often, they don't need growth hormone replacement as often, and they don't develop as many radiation-induced cancers; when you add up all the costs of these long-term side effects of x-ray therapy versus reducing those complications with proton therapy over that child's lifetime, then proton therapy becomes the far less expensive way of treating that child," said Dr. Foote.

Conclusion

According to some reports, proton therapy is expected to eventually replace the traditional methods of radiotherapy in the future.[1] But before that is even conceivable, more clinical studies need to show that the benefits of proton therapy outweigh the hefty cost of the treatment.

According to Dr. Rossi, cost not efficacy has slowed adoption of proton therapy. "The problem with protons has been the cost of building the facility," said Dr. Rossi. "Once the cost of proton facilities comes down, the cost of treatment will be similar to IMRT. At that point, there will be no doubt what treatment people would chose and that is treatment in the form of proton therapy."

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