Horizons in Proton Therapy
by Scot Fisher, DO; Evan Wuthrick, MD; Yan Yu, PhD, MBA; and Adam P. Dicker, MD, PhD

A Technology Timeline
Interest in proton therapy to treat human cancers began many decades ago. In the United States, the first patients receiving treatment with proton therapy were treated in 1954 at the University of California at Berkeley. Dedicated facilities to treat cancer with protons would take several more decades. In 1991 the first proton facility dedicated to patient care opened at Loma Linda University Medical Center in Loma Linda, Calif. Since that time five additional facilities have been opened in the United States at:
- Massachusetts General Hospital in Boston, Mass.
- The Midwest Proton Therapy Institute in Bloomington, Indiana
- The M.D. Anderson Cancer Center in Houston, Tex.
- The University of Florida Proton Therapy Institute in Jacksonville, Fla. (See article in May/June 2007 Oncology Issues.)
- ProCure Proton Therapy Center in Oklahoma City, Okla.

Worldwide 26 proton facilities are currently operational or near operational with at least 10 additional facilities in the planning and or construction phases.

Interest in developing and investing in proton facilities has increased over the past few years for several reasons, including the potential clinical advantage of the Bragg peak dose distribution of protons versus the classic high-energy X-ray distribution of photons. In theory this advantage allows a higher dose of radiation therapy to be delivered to a tumor relative to adjacent normal tissue compared to conventional photon therapy. Figure 1, page 24, illustrates the difference between a pristine proton beam, a proton beam with spread-out Bragg peak, and a photon beam in terms of dose build-up and fall-off versus depths in tissue. In addition, technical developments have improved accuracy and ease of use of proton beam therapy, such as a rotational gantry that enables treatment to be delivered in a similar manner to conventional X-ray therapy; high-quality imaging to identify the target volume; sophisticated treatment planning; and precise patient immobilization. Finally, while the financial investment into proton beam therapy is high, a successful proton facility can enhance the reputation of a radiation oncology department and potentially attract new patients into a dynamic cancer program.

Costs of the Technology
Compared to conventional external beam units, proton therapy facilities are very expensive. The cost of these projects can be broadly divided into three phases—planning, construction, and operations. Several vendors already have existing products on the market, and several other vendors are developing products for use within the next several years. In general, proton beam therapy vendors fall into two categories. The first category is those vendors selling multi-vault units of three or more vaults. The second category comprises vendors developing single or double vault units, which are considerably smaller. Multi-vault vendors currently have products available. Single-vault vendors intend to have products to market by the end of 2009 or in 2010.

Phase 1—Planning. This phase includes multiple steps and can take several years depending on the level of interest in building a proton facility. A team, including radiation oncologists, cancer center personnel, and administrators needs to address the:
- Feasibility of building a proton facility
- Vendor selection
- Land purchase (if needed)
- Selection of architectural and construction firms
- A financing structure.

For a proton facility containing three or more vaults at least four acres of dedicated land is required. Single vault units generally require 1,600-4,000 square feet. Depending on the type of unit selected, the cost of this portion of the project can range from several hundred thousand dollars to over $1 million. These estimates exclude the cost of any new land purchases. Generally, from the time you sign with a vendor to breaking ground is at least one year.

Phase 2—Construction. This phase is the most costly and can take several years to accomplish. Estimates for single-vault units range from $20 million to $30 million. Multiple-vault units are predictably more expensive. Depending on the number of vaults, the cost begins at about $80 million for a three-vault unit and increases as additional vaults are added. The building to house the proton facility is typically between 65,000-85,000 square feet, so construction costs are approximately $45 million. Finally, ancillary imaging equipment adds an additional $5 million to $10 million to the overall cost. Therefore the construction phase can range from $25 million to $40 million for a small unit to more than $140 million for a large freestanding facility.

Phase 3—Operations. The third phase begins when the first patient is
treated. Proton facilities have a projected life of 25 to 30 years. Staffing requirements will vary depending on the number of vaults. Typical recommendations include 1 to 1.5 physicists, 1 to 2 dosimetrists, and 2 radiation therapy technologists (RTTs) per vault. Routine maintenance and service require several service engineers. Service engineers could be either contracted with the vendor or separately employed as full-time employees of the proton facility.

**Outcomes of the Technology**

Due to technical factors and physician interests, the earliest proton therapy treatments focused on tumors of the orbit and base of the skull. Initially the major emphasis for proton therapy clinical research was dose escalation for tumors adjacent to critical normal structures that constrained X-ray dose that could be safely given and for which local tumor control with even advanced X-ray techniques was poor. Ocular melanoma is a prime example, and four large retrospective studies have been published that chronicle the experience of nearly 5,000 patients with ocular melanoma treated with 52-60 Cobalt Grey Equivalents (CGE) of proton therapy. In these experiences, local control and vision preservation compared favorably to other techniques, local control and vision preservation compared favorably to other treatment modalities and techniques including one study with a five-year local control rate of 96 percent. No randomized studies have compared X-ray or brachytherapy techniques against proton therapy for this disease.

Likewise, sarcomas of the spine and the base of skull are challenging to treat because of their proximity to the brain, brainstem, spinal cord, and optic structures. At Massachusetts General Hospital, 169 patients with chordoma and 163 patients with chondrosarcoma were treated with combined X-ray and proton therapy. Patients reported 94 percent local control for chondrosarcomas and 54 percent local control for chordomas. Osteogenic and chordogenic sarcomas of the axial skeleton have also been treated with combined X-ray and proton therapy, yielding a 100 percent local control for chordogenic sarcomas and 59 percent for osteogenic sarcomas in 47 patients reviewed by Hug and colleagues from Massachusetts General Hospital.

Ocular melanoma and spinal sarcomas are rare tumors; therefore, the business model for most proposed proton centers involves the treatment of common malignancies, such as prostate cancer. The X-ray treatment dose is limited by toxicity of the adjacent rectum and bladder. However, multiple well-designed randomized studies have shown a decrease in biochemical progression and increase in rectal toxicity when higher radiation doses are used. Investigators at Massachusetts General Hospital randomized 202 patients with advanced prostate cancer to either 67.2 Gy X-ray or 75.6 CGE using a conformal perineal proton boost. No differences between the two groups were found in overall survival or recurrence-free survival. However, the local recurrence rates at 7 years in the subset of patients with Gleason 9 & 10 histology were 63 percent on the proton arm and 15 percent on the X-ray arm. The men treated with protons also experienced a modest increase in the low-grade late sequelae.

Loma Linda and Massachusetts General Hospital cooperatively conducted a randomized trial of 393 patients with early stage prostate cancer to a 19.8 or 28.8 CGE “boost” followed by 50.4 Gy using 3D conformal techniques. Researchers found a statistically significant difference in 5-year biochemical failure rate (37.3 percent vs. 19.1 percent) favoring the arm receiving a total dose of 79.2 Gy. Notably, the dose escalation with protons was achieved without any increase in significant acute or late radiation toxicity. This data needs to be viewed in context. Other methods of achieving a “boost” include either a radioactive seed implant (temporary or permanent) or IMRT (intensity-modulated radiation therapy) alone. The data with these methods of dose escalation have achieved similar results to that of proton dose escalation.

Proton therapy may have the greatest theoretical benefit in pediatric malignancies. Dose distribution studies have estimated that utilization of proton therapy for rhabdomyosarcoma and medulloblastoma can reduce the incidence of radiation-induced second cancers by 2-15 fold. Clinical trials in pediatric glioma, medulloblastoma, rhabdomyosarcoma, retinoblastoma, and other malignancies are ongoing. The Agency for Healthcare Research and Quality (AHRQ) recently published a technical brief which concluded that a preponderance of available evidence suggests that proton therapy is safe and may provide effective tumor control, however their systematic review cites the “paucity of comparative evidence that demonstrates incremental value of [proton] therapy over conventional photon radiation therapy.” In addition, they suggest
that proton therapy may be a good alternative modality “for selected rare and specific types of cancer for which conventional treatments would cause substantial risk.” They also lament that no randomized trials have been conducted to directly compare the outcomes and toxicity of X-ray therapy versus the identical proton therapy dose in any pediatric or adult malignancy.

Reimbursement for the Technology
Proton therapy technical reimbursement is significantly higher than conventional IMRT. Daily CPT codes for proton therapy include:  
- 77520: Proton treatment delivery; simple, without compensation 
- 77522: Proton treatment delivery; simple, with compensation 
- 77523: Proton treatment delivery; intermediate 
- 77525: Proton treatment delivery; complex.

Examining any one of these codes is illuminating. For instance, Medicare reimbursement for CPT 77525 in 2005 was $850. This amount increased to a high of $1,390 in 2007 and has since declined to $841 for 2009. These dollar amounts are not adjusted for region and will thus vary in different parts of the country. These dollar amounts also do not reflect private payer reimbursement, although many private payers follow Medicare reimbursement rates.

Estimates for “break-even” revenue for a proton facility vary, depending on daily patient volume assumptions. Single-vault units need to treat between 25 to 35 patients per day, depending on the initial cost. A three-vault unit likely requires at least 75 patients per day. If reimbursement continues to decline then the break-even number of patients under treatment will increase unless the overall cost to build a facility has a similar decrease.

What Does the Future Hold?
Proton therapy is currently enjoying significant interest in the United States and around the world. Relative to other technologies available for the delivery of radiation therapy, the technology is very expensive. (A typical conventional linear accelerator unit in a freestanding setting costs approximately $5 million.)

The accuracy of treatment delivery with proton therapy faces many additional challenges compared to high-energy X-ray photon therapy (IMRT). Protons depend on the Bragg peak; however, this is affected by the amount and types of tissue the beam traverses. Whereas photon beams converge to a point in space (the “isocenter”), proton beam’s Bragg peak can overshoot or undershoot severely due to variations in air cavities residing next to organs or anatomic structures. Examples include: hollow areas in head and neck region, respiratory motion in lung cancer treatments, femoral bone angle, and bladder/rectal filling in prostate treatments. Variations in tumor size/edema, body weight, and CT intensity (denseness of tissue) can also profoundly alter where the concentrated proton dose is delivered. In practice, the distinct theoretical advantage of the proton Bragg peak is often not used directly to achieve maximum dose sparing of critical organs or maximum dose conformity to the tumor, because any over-shoot or under-shoot would cause deleterious effects to exquisite planning “on paper”. The theoretical advantages of protons are lost as the dose is “smeared” to achieve a degree of homogeneity to insure adequate treatment of tumor. At the present time with current treatment delivery technologies, IMRT appears more robust than proton therapy to these practical issues. In addition, competitive technologies, such as Cyberknife and Tomotherapy, are available in the same price range as accelerator-based delivery systems. In comparison, proton facilities can cost anywhere from $25 million to more than $140 million. Given the current economic environment, significant adoption of this technology is likely to require documentation of a therapeutic benefit to justify the cost. Hopefully well-designed clinical trials will add to the current body of literature and answer questions regarding therapeutic benefit.

References