Proton Therapy in an Era of Cost Containment

The fundamental goal of improving radiation therapy (RT) is to maximize dose to the tumor while limiting dose to normal tissues. Higher radiation dose to the tumor often results in better disease control, which can improve survival, and decreasing dose to normal tissues is always desirable.

Increased tumor doses and superior conformity indices have been achieved with several technologic advancements. The development of high-energy linear accelerators has enhanced the ability to reach deep-seated tumors while providing better skin-sparing. Improvements in treatment planning platforms and computational power have allowed for individualized CT-guided planning, whether it be “forward” planning (three-dimensional [3D] conformal) or “inverse” planning (intensity-modulated). Computer-assisted multileaf collimation has led to specific blocking of normal tissues for 3D conformal RT (CRT) and intensity-modulated RT (IMRT), both of which can be used to increase dose to tumor or decrease dose to normal tissue. Image-guided RT techniques, including on-board imaging with either orthogonal radiographs or CT scans, ultrasound imaging, and the use of tumor markers (fiducials), has increased the daily precision of RT delivery. Other advancements include the ability to either limit (controlled breathing) or actively monitor tumor motion (tracking) in real-time. Together, these enhancements have allowed for further dose escalation or hypofractionation of radiation using stereotactic radiation therapy (SRT) or stereotactic ablative radiation therapy (SABR). SRT/SABR further limit dose to normal tissues without the added toxicity of concurrent chemotherapy. Clinical evidence has shown improved efficacy with IMRT/SRT/SABR for certain sites, whereas the use of these modalities for other sites has been based on personal experience or the recommendations of national organizations.

Despite the advances outlined earlier, x-ray RT still has a relatively high exit dose (radiation dose beyond the tumor target), which can result in significant normal-tissue exposure. The cumulative RT dose to the patient is known as the integral dose. A higher integral dose may correlate with decreased quality of life (QOL), increased toxicity, and a higher risk of RT-induced second malignancies. In contrast, proton beam radiation therapy (PT) has a well-defined range of penetration into tissue. As protons enter the body, particles slow down and deposit a large portion of their energy near the end of their range with almost no exit dose. The resulting radiation dose distribution is known as the Bragg peak. Several dosimetric studies estimate that proton radiation can reduce radiation dose to adjacent normal tissue by approximately 50% compared with photon beams.

PT was initially considered for clinical use in 1946. The first patients were treated in the 1950s at medical physics laboratories in the United States and Europe that housed cyclotrons for particle acceleration. The Massachusetts General Hospital started using the Harvard Cyclotron Laboratory for patient treatments in 1961. The first hospital-based proton system designed specifically for patient treatments was implemented by Loma Linda University in 1990. Since then, 8 additional proton centers have opened in the United States, and as of June 2011, 36 proton therapy centers are available in Canada, China, England, France, Germany, Italy, Japan, Korea, Poland, Russia, South Africa, Sweden, and Switzerland. Thus far, more than 73,800 patients have been treated at these facilities. Although several additional centers have been announced, financing and development of these centers is very complicated, making the actual number of expected proton facilities difficult to predict.
The expansion of proton RT has been hindered by the high cost of building a new proton facility ($140–$200 million) and the need to recover these costs with high patient throughput. Many PT centers have a business pro forma that calls for a 16-hour treatment day. In general, the cost of treating a patient with protons can be 1.5 to 2.5 times that of photon irradiation. Moreover, no level I evidence exists proving the superiority of PT over x-ray RT (either 3D CRT or IMRT), although the widespread adoption of IMRT over 3D CRT was based on limited level I evidence. Furthermore, although PT is significantly more expensive than IMRT, IMRT is also more expensive than 3D CRT. This leaves one to question the scrutiny for PT today compared with the relatively uncontested adoption of IMRT just a few years ago. One possible answer lies within the title of this commentary—this is a new era of cost containment. Therefore, the high costs and complexity of PT may mark a potential dividing line and create an environment of “haves” and “have nots.”

Setting aside potential competitive biases for or against PT, a need exists to rigorously evaluate the added clinical value, if any, of this expensive modality. How can this best be done? Ideally, this process would begin by documenting the theoretical benefit. In RT, this can be achieved through a dosimetric, or treatment planning, study. Several of these studies documenting the theoretical benefits associated with PT over x-ray RT have been published in the literature for several disease sites, including lung, prostate, and brain. This theoretical benefit would then be tested in a phase I or II trial. However, far fewer of these studies are reported in the literature. Finally, PT would be tested against x-ray RT in a phase III study to prove a measurable benefit. The incorporation of financial metrics into these studies would also help determine whether the benefit seen with PT can justify its cost.

A methodical approach to studying the use of PT in lung cancer is underway. During the past year, key papers from the MD Anderson lung group have suggested that patients with lung cancer treated with PT, particularly those with stage III disease, may have improved survival and toxicity compared with those treated with x-ray RT. The MD Anderson and Massachusetts General Hospital groups are currently conducting a phase III study of PT versus x-ray RT for patients with stage III lung cancer. This is believed to be the first phase III study comparing PT with x-ray RT, and it has the potential to be practice-changing if PT reflects positive results.

The use of PT is most frequently debated in prostate cancer, particularly because considerable controversy already exists regarding appropriate use of more standard treatment modalities and because of the advent of expectant management, which avoids treatment altogether. The theoretical benefits of PT (decreased rectal dose, decreased bladder dose, and the potential of dose escalation) seem to be attractive to many men, who have been highly motivated in seeking out and traveling to PT centers for treatment. Although some insurance companies require comparisons between IMRT and PT plans for prostate cancer treatment approval, CareFirst BlueCross, BlueShield, and others consider PT “medically necessary” and allowable for the treatment of prostate cancer if physicians believe it is indicated.

However, near-unanimous agreement exists that PT is an ideal RT modality for children and specific central nervous system tumors, despite the absence of any level I evidence. In fact, the Children’s Oncology Group (COG) is the only North American cooperative group sponsored by the NCI to allow the use of PT in its clinical studies.

Aside from assumptions that PT is superior to RT, how can improvement be measured? In some cancers it is based on “hard outcomes,” such as survival. Other surrogates of improvement include tumor markers (prostate-specific antigen), toxicity,
and QOL. What if clinical trials show that protons improve survival, tumor control, and QOL, and result in decreased toxicity and risk of second malignancy? How much of an improvement justifies the increased cost of PT versus x-rays? If trials confirm the superiority of PT over x-ray RT, is it ethical to limit access of this technology to only those who can afford it and are allowed access/reimbursement through their insurance company?

The ideal method of answering these questions are well-developed prospective clinical trials that address these important clinical questions. It will, however, take commitment by PT centers, patients, and payors to design, accrue, and complete prospective clinical trials. In the interim, how should insurance companies determine whether they will allow proton versus photon treatment? Should it be on a case-by-case basis or should it be determined by tumor site? Many insurance companies consider PT to be experimental, and therefore proton facilities are rarely granted permission for a peer-to-peer review. Other payors have started using radiation oncology benefit managers (ROBMs). ROBMs are used by insurance companies to control use of high-tech imaging modalities, such as PET and MRI, and more recently to control use of expensive radiation treatments, such as IMRT, SABR, and PT. Whether ROBMs truly control costs is currently unclear, and based on an American Society for Radiation Oncology (ASTRO) position statement in September 2009, integration of ROBMs in radiology and radiation oncology results in preauthorization, which “delays patient care” and “serves as a barrier to the doctor-patient relationship.”

Rather than wait for a peer-to-peer review to be requested by ROBMs, the Department of Radiation Oncology at the University of Pennsylvania has taken matters into its own hands by negotiating radiation payments with payors and prospectively producing IMRT and PT plans for various sites. They only treat patients with protons if the plan is superior to the IMRT plan. These proactive approaches may expedite coverage decisions and eliminate the need for ROBMs, thus freeing up additional resources for prospective clinical trials. One critique of this approach, however, is that it is based on an assumption that small alterations in dosimetry directly translate into improved cancer outcomes or reduced side effects. Data from a direct comparison with IMRT for the treatment of prostate cancer do not yet exist to support this assumption.

Given that more than 74,000 patients have been treated at various centers, another option is to combine retrospective data and perform multivariate and comparative analyses to help determine the potential benefit of PT. Because it is unrealistic to expect that an appropriate clinical trial exists for every cancer patient, practitioners at the University of Pennsylvania and others have created a prospective registry to collect clinical data, tissue/blood samples, and patient self-reported QOL to compare PT with other modalities. Dr. Stephen Hahn, chair of the radiation oncology department at the University of Pennsylvania, concedes that although “registries don’t ask a specific question, they do provide additional data to assist in determining which patients are more likely to benefit or not benefit from proton therapy.”

Other centers are also trying this approach. Dr. Sameer Keole, Medical Director of the ProCure Proton Therapy Center in Oklahoma City, says that he has offered the same concept to insurers. “We would like to be engaged in true coverage with evidence development with the carriers. We understand and respect their position on proton therapy, in respect to both efficacy and costs. We feel that we have an obligation to work with them to prove the value of proton therapy.” To this end, Keole’s center, along with the ProCure center in Chicago, has developed a robust infrastructure to capture data prospectively through a combination of electronic medical records and
databases. Approximately 90% of patients are enrolled on some type of prospective protocol, and the 2 centers have been able to report early outcomes at peer-reviewed meetings. “While we are actively engaged in open and constructive dialogue with insurers, we have not had the same success in coverage as other proton centers have had.”

In a 2008 editorial, Goitein and Cox suggested that once proton beam therapy becomes clinically available, those who advocate for photon therapy should show that “cost savings achieved by using x-rays are not accompanied by undesirable additional morbidity.” They also point out that given existing data, “there is a high probability that protons can provide superior therapy to that possible with x-rays in almost all circumstances.” Dr. Hahn, however, believes that “in some sites and/or patients, proton treatment may not be superior (homogeneity/biology) and we need more data before widespread use of protons can be accepted.” In addition, some practitioners believe that it is unethical to expect some patients to receive photon therapy, and that patients will refuse to enroll on clinical trials randomizing them between protons and x-rays. However, in a “willingness to participate study” conducted at the University of Pennsylvania, preliminary assessment shows that a significant number of patients with prostate cancer would agree to be enrolled in a randomized study for PT.

The ASTRO position statement opposes the use of ROBMs and oversimplified guidelines when determining radiation insurance coverage policies, and instead recommends that payors follow guidelines such as the American College of Radiology (ACR) appropriateness criteria and NCCN Clinical Practice Guidelines in Oncology. However, given the limited data on protons, even these guidelines are unclear for most tumor sites. These ambiguities not only apply to proton beam therapy but also exist for IMRT and SABR. Perhaps rather than investing in ROBMs, insurance companies could work with (instead of against) radiation oncology facilities to initiate prospective trials/registries to truly quantify the potential benefits of newer radiation delivery modalities, including PT. Had this been done 10 years ago, a vast amount of data would be available to compare new technologies. When asked about supporting PT clinical trials, Dr. Daniel Winn, Vice President of CareFirst, acknowledged, “We would be very much in favor of supporting clinical trials to test the efficacy of PT and other modalities. In the end we just want the evidence so patients can get the best care.” However, he admits that the true challenge is convincing some of the “self-insurers” to follow suit and also support clinical research.

If insurance companies and radiation facilities work together to develop well-designed clinical trials and registries, high-quality radiation treatments can be offered to all patients in an efficient, cost-effective manner without eroding the doctor–patient relationship. If this occurs, the hope is that 10 years from now, commentaries such as this will be unnecessary.

References
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