ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Current and Future Status of Proton-Beam Radiation Therapy in Radiation Oncology

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H&O What is proton-beam radiation therapy?

JC Proton-beam radiation therapy (PBRT) is a form of radiation therapy that shares common characteristics with x rays as far as the interactions in biologic systems. There is no major distinction between the biologic effects of protons and x rays. The major difference between these two forms of radiation therapy is in how the dose of radiation is distributed in the body. For x rays, no matter how high or low the energy of the dose, the maximum dose the patient receives is close to the surface of the skin (or 2–3 cm beneath the surface), and the radiation beam then penetrates through the body. It is well known that the x rays used for imaging penetrate through the body in order to produce an image on film on the other side of the body from their source. However, these x rays have very low energy in comparison to those used therapeutically. With PBRT, the beams enter the body with a lower dose and the maximum dose is delivered at some depth in the body depending upon the energy of the proton beam. After the protons come to a stop in the body and deposit all of their energy, no radiation passes through the rest of the body. PBRT deposits the energy in what is called a Bragg peak, named for the Nobel Prize–winning scientist who discovered that charged particles interact in this way in the body. This peak distribution can be shaped to be the size of the tumor. The peak is typically sharp, only a few mm in width, but it can be modified to be as wide as 10–12 cm. The Bragg peak is shaped using devices outside the body. One is called an aperture, which is a piece of brass with a hole in the middle molded to the same shape as the tumor; another piece, made of acrylic, absorbs the proton beam so that when it deposits the energy inside the body, the proton energy has the shape and size of the tumor. The dose can be refined by changing the energy of the beam, which determines how deep it penetrates, and by changing the shape of the beam, which determines the shape of the high-dose area inside the body. In other words, it is possible to give a very high dose to a tumor and yet avoid all of the structures beyond the tumor and deliver a dose to the surface of the skin that is lower than that given to the tumor. The doses can be escalated to improve tumor control while avoiding effects in normal tissues relative to x rays.

H&O How does the experience of receiving PBRT compare to that of other forms of radiation therapy?

JC The number of treatments a patient receives is approximately the same as it is for treatment with x rays. In time, as we learn more, it may be possible to give higher doses per treatment and reduce the number of treatments, but we are not comfortable doing that yet. Right now the same number of treatments are given with PBRT as with other radiation modalities—anywhere from 20 to 40 treatments, depending on the disease. PBRT is administered 5 days per week for 4–8 weeks. For each individual treatment, the set-up time is comparatively longer with PBRT because the patient is positioned very precisely and images are taken each day in order to confirm that the positioning is perfect. The proton beam is actually on for approximately 2 minutes. We treat from two, three, or four different directions in order to sum the dose at the precise location of the tumor and to try to avoid normal tissues. Because each treatment field has a separate set of devices, the devices must be changed in the head, called the snout, of the proton equipment between each treatment. Overall, the simplest treatment takes 20 minutes and more complex treatments take 30 minutes. The patient feels nothing other than whatever discomfort results from being immobilized for that period of time.

H&O What is the current status in terms of the availability of PBRT in the United States?

JC At the present time, there are four hospital-based proton facilities. The facility at Loma Linda University in California has been in place the longest, treating since 1991. Another facility is at Massachusetts General Hospital, a carry-over from their long-term experience at the Harvard Cyclotron Laboratory; that facility has been treating since 2001. Here at the University of Texas M. D. Anderson Cancer Center, we started treating in May 2006. The University of Florida in Jacksonville started treating in August 2006. These are the only facilities in place so far. There are treatments delivered at a couple of research facilities in the United States, one at the cyclotron at the University of California in Davis, which treats only eye tumors, and another at the University of Indiana in Bloomington. Those are both very small operations.

H&O In what disease settings is PBRT used?

JC Overall, there have been more than 45,000 patients treated around the world with PBRT. Historically, because most of the treatments have been carried out at physics research facilities around the world, where the physicists would allow the equipment to be used for brief periods of time, the vast majority of patients treated with proton beams have had uveal melanoma, a very rare tumor of the eye. More than 20,000 people have been treated for uveal melanoma, which can be treated in 1 week. The amount of time that can be set aside for patients to be treated at these physics facilities was very clearly defined and the patients could be lined up to receive 5 days of treatment. This treatment modality has also been used, mostly at the Harvard Cyclotron Laboratory, for tumors at the base of the skull, particularly chondrosarcomas, cartilaginous tumors, and chordomas. It has also been used for tumors immediately adjacent to the spine, where it was necessary to avoid irradiating the spinal cord. The next largest group of patients treated are those with cancer of the prostate. There have been at least 2,000–3,000 patients treated for cancer of the prostate with PBRT, with good results as far as tumor control, though not necessarily better than the results seen with x rays. With PBRT, however, there are fewer side effects. With standard x-ray techniques for prostate cancer, as were used 20 years ago, grade 3 or higher side effects on the bowel and bladder occurred in close to 15% of patients. With modern x-ray techniques, that level has been reduced 1–3%, and with protons, it is 1% or less.

H&O Does PBRT avoid the risk of second cancers?

JC Second cancers are a function of the disease treated. Data on second cancers with tumors at the base of the skull are scant, and the risk of second cancer associated with cancer of the prostate is low. Nevertheless, there is a theoretical risk of second cancer. This risk should be at least as low or lower with PBRT than with x rays because the x-ray treatment delivers radiation to a larger volume of tissue.

H&O Has PBRT been used in the pediatric setting?

JC The pediatric setting is one of the major indications for PBRT because in children, any organ or tissue that is still growing is very sensitive to radiation effects. The long-term consequences can be quite profound. Growth abnormalities in muscle and bone are a great concern in children. Therefore, PBRT is often preferred in children because of the ability to avoid normal tissues. One of the more common brain tumors in children, medullablastoma, with which it is necessary to treat the entire brain and spine to encompass the entire central nervous system, is associated with significant long-term side effects when treated with x rays. With conventional x-ray treatment, the x rays penetrate organs in the body such as the heart and lung, as well as the esophagus, bowel, and ovaries, whereas protons treating from the back can be stopped directly in the vertebral body and avoid irradiating all those structures. Additionally, even though proton therapy is more expensive when it is given, the avoidance of these long-term effects may lead to lower long-term costs with PBRT than with x-ray therapy.

H&O Has PBRT been compared to other types of radiation therapy in terms of efficacy?

JC This comparison has occurred to a limited degree. There have been no pure studies of PBRT versus x rays. There are some studies that have used x-ray therapy and then proton therapy as a sort of boost for cancer of the prostate. But there has not been a head-to-head comparison of PBRT with x-ray therapy. There have been historical comparisons in certain diseases. For example, in patients with chordomas and chondosarcomas at the base of the skull, results of treatment with x-ray therapy and PBRT have been compared. PBRT has proven to be more effective. These studies, however, were not randomized; those malignancies are sufficiently uncommon that it would be difficult to conduct a randomized study. Our institution is eventually going to conduct a comparison of PBRT versus our most advanced form of x-ray therapy, which is intensity-modulated radiation therapy, in lung cancer, for which we have enough patients.

We have conducted many comparisons of the dose distributions between x rays and protons in various disease categories. Our work in looking at the effects on normal tissues with x rays has given us a great understanding of what total doses, and what volumes of normal tissue receiving the dose, are associated with side effects. For example, in the chest, if we are treating the esophagus or the lung, we have studied what the risk of side effects is with different doses and volumes of normal lung irradiated. When we do comparisons of the x-ray dose distributions with the proton dose distribution, we can show over and over again that PBRT avoids the normal tissues better than x rays in many disease sites. Studies of this so-called comparative dosimetry have taken place in many different disease sites. I believe this type of comparison is one specialists in other fields are not used to considering. It requires a little understanding to see the relationship between side effects and dose distributions. It is possible to do comparisons of dose distributions using two different techniques, specifically protons versus x rays, and to show that normal tissue can be avoided with PBRT, reducing the risk of side effects.

H&O What developments do you anticipate in the future with PBRT?

JC A primary interest is combining PBRT with chemotherapy. Many of the patients who require high radiation doses can also benefit from chemotherapy given at the same time. As we can avoid irradiating the normal tissues, which would otherwise give rise to side effects during the course of treatment, we can reduce the risk of toxicities. The side effects are greater when we combine chemotherapy and radiation therapy, but the tumor control is quite good. If the tumor control can be maintained while reducing side effects, we will have added a powerful combination therapeutic modality to our armamentarium. Work has begun in this direction. Some very preliminary data exist with a small number of patients treated and analyzed to suggest that this combination modality is very promising.

There is a good deal of interest around the nation, at academic centers and even at private practices, in developing facilities that can administer PBRT. The initial costs are high, so it is necessary to figure out how to pay for the development of such a facility. Our facility, which has four treatment rooms, an experimental room, and an imaging suite, which makes it a very complete facility, was slated to cost $125 million when its construction begun. The price since then for such a facility has surely risen. The University of Pennsylvania is building a facility right now, and there are many other institutions that are discussing building their own facilities. I believe that the value of PBRT is beginning to be appreciated more widely due to articles published about comparative dosimetry as well as the investment made in the facilities around the country thus far.

Suggested Readings

Chang JY, Zhang X, Wang X, et al. Significant reduction of normal tissue dose by proton radiotherapy compared with three-dimensional conformal or intensity-modulated radiation therapy in Stage I or Stage III non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys.* 200;65:1087-1096.

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