Prostate Cancer Foundation

ADVANCES

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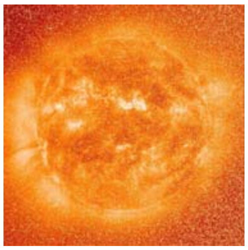


Protons: Powering Our Sun and New Opportunities for Radiotherapy

While this summer issue of *Advances* is not being written on the beach, I can occasionally catch the scent of a sea breeze with the western facing windows of my office open. So, in the spirit of sunny and summer thinking—and because we are frequently being asked online about *proton therapy* for early prostate cancer, I am focusing this issue of *Advances* on an aspect of nuclear energy that powers our sun, warms our beaches, and is involved in treating prostate cancer.

PCa Radiation Therapy 1995 to Present

Radiation therapy is the treatment of cancer patients with energy that kills cancer cells. These cells are more sensitive to radiation than normal, non-cancerous cells. The *differential sensitivity* of tumor cells to radiation therapy compared to normal cells is one of the fundamental hallmarks of human cancer. Without much fanfare, radiation therapy for patients with early-stage prostate cancer has continued to improve over the last decade. While more may not always be better, it appears (for reasons still being researched) that prostate cancer cells do require more energy, and thus more trips to the radiation oncologist, to kill them compared to many other tissues.

Multiple clinical trials in Europe and the U.S. between 1995 and 2009 demonstrated that higher doses of radiation are more effective in controlling early prostate cancer. For example, Professor David Dearnaley (with whom the PCF met at London's The Royal Marsden in the summer of 2008) reported the results of a UK Medical Research Council trial of "dialing up" the total dose from 64 Gy to 74 Gy in 843 men with localized prostate cancer who received hormonal therapy in combination with external radiation. At five-years after treatment, the prostate cancer disease-free survival rate was superior in the higher radiation dose arm: 71 percent disease-free versus 60 percent disease-free in the lower dose group.

Defining a Gray (Gy)

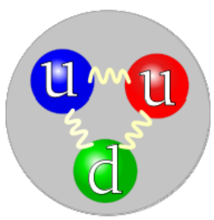
$$1\ \mathrm{Gy} = 1\ \frac{\mathrm{J}}{\mathrm{kg}} = 1\ \mathrm{m}^2 \cdot \mathrm{s}^{-2}$$

A Gy (gray) is how radiation is dosed. One Gy is the absorption of one joule of energy, in the form of ionizing radiation, by one kilogram of matter.

Many patients hear the word “rads” in their journey through radiation therapy; 100 rads are equal to 1 gray. In general, the doses of radiation used today in major academic centers are on average 10 to 20 percent higher in rads than those prescribed a decade ago. Part of the success in improving survival from prostate cancer in the past 15 years has been attributed to improvements in radiation therapy. One of these advances is using protons to deliver high radiation doses to a prostate tumor while “pushing the dose”.

Why Protons Are Different

Protons deliver their radiation energy differently than x-rays. Unlike x-rays, a beam of protons has a low “entrance dose” (the dose delivered from the surface of the skin to the front of the tumor) and a high dose designed to cover the entire tumor. In addition, there is no “exit dose” beyond the tumor. Theoretically, these characteristics should give proton therapy the ability to deposit a radiation dose in a more precise way while minimizing damage to the surrounding normal tissues. Thus, proton radiation is an emerging therapy for localized prostate cancer utilized by some radiation oncologists and increasingly sought by patients.



The Proton Structure

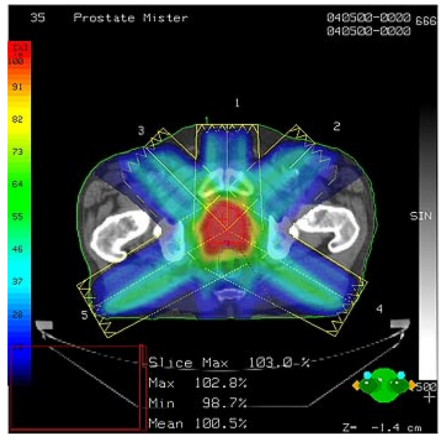
A proton is a positively charged particle. A proton is found in atoms and is a subatomic particle with an electric charge of +1 elementary charge. Protons are found in the nucleus of each atom but are also stable by themselves and are also known as the hydrogen ion, $^{1}H^{+}$. Protons themselves are composed of 3 even more fundamental particles comprising two up quarks and one down quark. (The lesson in quantum mechanics ends here.)

Currently, intensity modulated radiation therapy (IMRT) is the most widely used form of external radiation for prostate cancer in the U.S. and developed countries. IMRT is an advanced approach to delivering beams of radiation with greater precision. To achieve this result, computer-controlled linear accelerators deliver precise radiation doses to a malignant tumor or specific areas within the tumor. IMRT allows for the radiation dose to “conform” more precisely to the actual three-dimensional shape of the patient’s individual tumor. The surrounding anatomical structures like the bladder and the rectum also have unique shapes and the treatment can be designed to lower exposure to these structures in each patient. The shape and size of the tumor is defined using computed tomography (CT) scans prior to commencing treatment. The “conformation” of the radiation dose to tumor parameters is achieved by changing or modulating the intensity of the radiation beam in multiple small volumes within the tumor. IMRT allows higher radiation doses to be focused on regions within the tumor, while reducing the dose to surrounding normal tissues and structures.

Most radiation oncologists have conducted clinical trials that demonstrate that IMRT also has the potential to reduce treatment toxicity, even when doses are not increased.

Dosing & Conforming for IMRT

IMRT treatment has to be planned carefully using 3-D CT images of the patient's anatomy, along with computerized dose calculations to determine the optimum dose intensity pattern that will best conform to a tumor's shape. Usually, combinations of several intensity-modulated fields coming from different beam directions produce a custom tailored radiation dose. The use of a large number of beams during IMRT delivers a low dose to larger volumes of normal tissue than conventional radiotherapy.



A 3-D tumor image slice captured by computed tomography (CT)

IMRT is the current standard of care to which proton radiation must be compared, as it is being used most extensively to treat prostate cancer, head and neck cancers, and cancers of the central nervous system. IMRT has also been used to treat more than 12 other cancer types, including pediatric cancers.

Proton therapy has many early advocates. For example, see: http://www.protons.com. Currently, both IMRT and proton radiation have the potential to increase whole body radiation exposure. Because IMRT employs multiple treatment fields, it exposes a greater volume of normal tissue to low doses radiation. Theoretically, longer treatment times might also increase total body irradiation as a result of leakage from what is called by radiation oncologists, the treatment head. A lower lifetime risk of a secondary cancer in the radiation field would be expected to be associated with proton therapy as this form of radiation exposes less normal tissue to radiation. Secondary malignancy is a major concern in younger patients, but is less of an issue for older patients. There is a very long period for the development of a secondary cancer if one arises (10–20 years). Most radiation oncologists treating prostate cancer patients share with them the fact that the latency period for developing a secondary cancer in the field of radiation far exceeds the life expectancy of most men treated for prostate cancer. For pediatric oncology patients and younger men considering radiation therapy for early prostate cancer, however, the lifetime risk of a secondary malignancy in the treatment field has influenced choices towards proton therapy.

More Trials Data are Needed

By a search of the National Library of Medicine there are 203 research papers published in the literature on "proton therapy for prostate cancer". Searching for "comparison of proton therapy and IMRT for prostate cancer" there are only 11 total reports. There are no comparative, randomized clinical trials published yet in early prostate cancer comparing IMRT to proton therapy that assess a superior "cure rate" or "prostate cancer disease-free survival" for protons—or decreased bladder and rectal side effects for protons over IMRT. So far, the early evidence that side effects from proton therapy are fewer for patients are preliminary. So until such a trial is conducted, the superiority of protons over IMRT is a matter of informed debate and health care economic writings.

Accelerating protons for use in treating cancer is an exceptionally expensive proposition. Proton therapy needs heavy equipment (cyclotrons) developed originally in centers studying particle physics. The accelerators are huge capital investments. For instance, the Orsay proton therapy center in France uses an accelerator that weighs 900 tons in total. According to Wikipedia, there are now proton therapy centers in Canada, China, England, France, Germany, Italy, Japan (5 centers), Korea, Russia, South Africa, Sweden, Switzerland, and the United States. These have treated more than 60,000 cancer patients so far.

According to the National Association for Proton Therapy, there are six proton facilities currently operating in the U.S. with four more under construction and others in the development stage (see http://www.proton-therapy.org/map.htm). The business model for many of these centers (except for centers specializing in children's cancers) is based on treating a high number of prostate cancer patients annually whose insurance will cover the treatment cost. The upfront cost of building these centers is estimated from $25 million on the low end to $150 million on the high end, depending on the number of treatment suites constructed.

As efforts are made to reduce the size of these machines, the cost to build them and the price tag for treatment will also fall—giving cancer patients more accessibility to this treatment option. A machine now being developed by researchers at Lawrence Livermore National Laboratory will be a fifth of the size and cost of the proton therapy machines that are currently in use. This next generation of proton equipment is still on the distant horizon.

Justifying the Cost

The issue of whether the cost of proton therapy for prostate cancer is justified in healthcare economics has generated its own academic literature and "comparative effectiveness" has already been directed towards protons. As the technology is new and there are no large scale clinical trial data that indicate a clear clinical advantage of protons over IMRT in survival, emphasis has been placed on side effects. According to a recent review of all published literature from Professor Anthony Zeitman, MD, at Harvard Medical School, there are no published data to support the concept that protons allow a safer increase in total dose than IMRT. While there are clinical impressions that protons confer lesser side effects, the bladder, neck and anterior rectum receive similar doses to similar volumes when either IMRT or protons are used. More "quality of life" research is ongoing in patients in the months and years following treatment to assess whether later side effects are lessened with protons.

Professor Andre Konski, MD, director of clinical research in the Department of Radiation Oncology at Philadelphia's Fox Chase Cancer Center, performed an economic analysis to determine whether proton radiation was cost-effective in comparison to IMRT. A model was used to calculate the incremental cost per quality-adjusted life year (QALY) of proton therapy versus IMRT for a man with intermediate-risk prostate cancer. The model assumed that IMRT would be delivered to a dose of 81 Gy and result in a five-year disease-free survival of 83 percent, whereas use of protons would allow delivery of 91.8 Gy and yield a 93 percent five-year, disease-free survival with no increase in short-term or long-term side effects. Their model used estimated costs of $58,610 for proton therapy and $25,846 for IMRT.

The incremental cost-effectiveness ratio was calculated to be $63,578 per QALY for a 70-year-old man and $55,726 per QALY for a 60-year-old man. Whether one agrees or not with healthcare economists, the commonly accepted threshold is $50,000 or less per QALY for a medical procedure to be widely utilized, on an economic basis, in most developed countries. As the healthcare debate continues at this writing, the high cost of proton therapy could be a major impediment to widespread utilization in the coming years unless technology itself can decrease this cost.

Potential Proton Benefits for SBRT

Stereotactic Body Radiation Therapy (SBRT) is another approach that can deliver enormous radiation doses to a tumor. A stereotactic radiation treatment for the body employs a three-dimensional coordinate-system for the exact localization of tumors in the body in order to treat them with limited and highly precise treatment fields. Protons delivered through SBRT might be a superior means of delivering higher doses and fewer total treatment sessions while sparing vital structures such as the urethra, bladder and rectum. Theoretically, fewer dose fractions might lower the cost of proton beam therapy to the health system. Clinical research in this area is currently being conducted in a few centers.

Using PET and CT to Monitor Proton Delivery

Proton radiation leaves a trail of positron emitters along the beam path that can be detected using either a PET or CT scan shortly after delivery of a radiation dose. This favorable property of proton beams might also be used as a quality assurance tool for verifying total treatment of the tumor and enhancing outcomes.

Conclusions

There has been expanding interest in proton therapy for pediatric tumors and those of the central nervous system. More recent enthusiasm for this modality relates largely to its potential as a treatment for early prostate cancer. Where available, proton radiation has been recognized as an effective new tool in the management of prostate cancer and is now one of several methods used to deliver high-dose radiation to the prostate. Where patients can access proton therapy, it is a good choice. So far, there are strong inferences but no hard clinical evidence that—at current levels of sophistication—proton radiation is superior to the more widely used IMRT. Current economic analysis indicates that protons, as currently used and priced, are likely to draw strong opposition from cost proponents. However, as was seen with the introduction of CT and MRI technologies 20 years ago, technology advances and market penetration can change the cost factor. As more research is reported on the clinical value of protons, the overall equation may change. We will keep you updated.