A NOTE OF THANKS FROM THE EDITOR

On behalf of the PAACT staff we would like to thank our members, advocates, professionals, donors, sponsors, corporates, and foundations that participated in the large fund raising effort that took place during December, 2006. As noted in our March financial statement you will find the year end report for 2006. Total revenues at $202,644.97, total expenses for the year at $192,753.60. Because of your generosity we had our second largest December since 1993 with donations topping out at $66,050.03. The overall result is that 2006 total revenues finished $9,891.37 ahead of total expenditures. Congratulations and thank you to each and every one of you, we could not have done it without you.

CONFORMAL PROTON BEAM RADIATION THERAPY OF PROSTATE CANCER

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Introduction
External beam radiation therapy is one of the commonly employed curative treatments for prostate cancer. The term “External Beam,” refers to the fact that the radiation used for treatment is generated by a machine which is external to the body. This distinguishes external beam radiation from brachytherapy, in which small radioactive sources are actually inserted into the prostate gland. With few exceptions, “External Beam” implies treatment with x-rays for it is x-ray therapy which has been the mainstay of radiation treatment since its inception in the late 19th century.

Over the last fifteen years, a new type of external beam radiation therapy, proton beam radiation therapy, has become available at a few select centers in the United States and abroad. This treatment employs subatomic particles to deliver high doses of radiation to a variety of cancers, including prostate cancer[1]. The rationale and desire to treat with protons is based on their physical superiority to x-rays. Simply put, a proton beam will stop at some point within the body, while x-rays will not. From a clinical standpoint, this unique aspect of proton beam radiation allows the radiation on-
cologist to reduce the normal tissue radiation dose to levels which are not possible with any type of x-ray therapy (including Intensity-Modulated Radiation Therapy and Tomotherapy) while simultaneously escalating the radiation dose to the target tumor. In the following paragraphs, I will briefly illustrate the physical differences between protons and x-rays, discuss the history of their use in prostate cancer treatment, and cover clinical results to date.

The Differences Between Protons and X-Rays
In order to understand the potential advantages of proton beam radiation therapy, it is necessary to delve somewhat into the fundamental physics of x-rays and protons and their interactions with human tissue. X-rays are, essentially, high energy forms of visible light. X-rays are massless, and do not possess an electric charge. Because of this, they are highly penetrating and it is indeed their ability to penetrate the human body which makes them such useful diagnostic tools. As an x-ray beam enters the human body, the energy of the beam is rather slowly dissipated by interacting with bone and soft tissue. However, there is typically some energy which passes completely through the body. If the goal is diagnosis, this is a useful property because it is the x-ray energy which leaves the body that can be captured and analyzed to provide a picture of the internal organs along the beam’s path. However, what is desirable in diagnosis is not necessarily desirable in therapy because that same beam is delivering radiation to everything within its path, be it normal tissue or tumor. Again, this is true of all types of x-ray therapy including IMRT - while with IMRT we can vary the intensity of the beam so that the dose rate as the beam passes through particularly critical normal tissues may be low, what we cannot do, and what is indeed impossible to do, is to get that x-ray beam to stop within the body. IMRT in fact represents the latest in a series of elegant compromises between the radiation dose we want to give to the tumor and that which the normal tissue will tolerate - it reduces the volume of normal tissue receiving a high radiation dose at the expense of increasing the volume of normal tissue receiving low to moderate radiation doses. What would be ideal, from a treatment standpoint, would be a form of radiation which would deliver zero dose to the tissues in front of the target, 100% dose to the target, and zero dose beyond the target and this ideal is and always will be an impossibility with x-rays.[2-5].

It is, however, far more achievable with protons. A proton is a subatomic particle with a discreet mass and an electric charge, and these two properties radi-
cally influence the proton-human tissue interaction. When a beam of high-energy protons enters the human body, the radiation dose delivered to tissues proximal (in front of) the target is low, because at that point the protons are still traveling with a high velocity and therefore have very little interaction with the tissue they are passing through. By attenuating the beam so that the protons are brought to a stop as they pass through the target (this is accomplished by passing the beam through a series of patient-specific anatomic compensators before the beam enters the patient) the radiation dose to the target is maximized, and since the protons (by virtue of exhausting their kinetic energy) come to rest just beyond the distal (far) edge of the target, the "exit" dose is zero. From a practical standpoint, the "integral dose" (total dose to normal tissue) in a proton beam treatment plan for prostate cancer is three to five times less than that which is common when sophisticated x-ray therapy plans (utilizing IMRT) are employed. Again, this reduction in normal tissue dose means that the radiation dose given to the tumor can be increased with relative safety, and indeed the benefits of such dose-escalation in early stage prostate cancer will be discussed shortly[6, 7].

Like many medical breakthroughs, the potential superiority of protons over x-rays, and their utility in radiation therapy, was recognized not by a physician, but by a scientist from another discipline. Physicist Robert R. Wilson, then a professor at Cornell University (and later the founding director of the Department Of Energy’s Fermi National Accelerator Laboratory, one of the world’s premier physics research institutions) had the insight to propose, in a seminal 1946 paper{Wilson, 1946 #4749} their use in cancer treatment. However, again like many other ideas, their routine use required the development and maturation of other technologies before the theoretical advantages of protons could be exploited in clinical medicine.

**Early Clinical Work**

Although initial treatments of intracranial cancers began in the late 1950’s, proton beam radiotherapy of prostate cancer commenced in 1977, when Dr. William Shipley and colleagues at the Harvard Medical School began a study in which patients with advanced prostate cancer received some of their radiation treatment via a proton beam “boost” delivered in the hope that by giving a higher dose of radiation than was possible at the time with the x-ray therapy equipment then in existence, they may improve the control rates of such advanced tumors without creating unacceptable side effects. Since at that time dedicated proton beam medical treatment facilities did not exist, the patients were treated in Cambridge at the Harvard Cyclotron Laboratory, utilizing a machine which was primarily employed in high energy physics research. The initial results of what was in effect a toxicity trial were published in 1979 and demonstrated that the technique could be performed in safety and with acceptable side effects{Shipley, 1979 #4739}.

These encouraging results led to a larger trial, in which again patients with locally advanced bulky prostate cancer (stage T3 and T4 disease) were randomly assigned to receive either a) a radiation dose of 67.5 Gy to the prostate, delivered entirely with x-rays or b) a total dose of 75.6 Gy, delivered with a combination of x-rays and protons, the latter being incorporated to “boost” the radiation dose to the prostate. Because of the limited number of patients who could be accommodated on the Harvard Cyclotron, patient accrual was slow and in fact, over a period of over a decade, just over two hundred patents were enrolled and treated on the trial.

The results of the trial were published in 1995[8]. Although the overall survival was no different between the two treatment groups (primarily because of the high rates of metastatic failure in both groups, which was a consequence of the advanced stage of the patients at diagnosis), the incidence of local (i.e., prostate) failure was lower in the high dose group, and this trend was most significant in those patients with the highest grade tumors (Gleason 8-10). This finding led credence to the concept of dose-escalation as a means of improving prostate tumor control, and directly led to the eventual creation of a clinical trial to test this hypothesis.

**Development of Hospital-Based Proton Beam Treatment Facilities**

Although the aforementioned physical advantages of protons over x-rays are easy to demonstrate, their use in clinical medicine was limited by the lack of treatment centers dedicated to their use in a medical, not laboratory, setting. Why was this so? Because in order to accelerate protons to the velocities necessary for human treatment (roughly one-half of the speed
of light) one must construct purpose built “Atom-Smashers” (either a cyclotron or synchrotron) that are far more complex in their construction, operation, and maintenance than the linear accelerators used for x-ray therapy. Until 1990 such equipment was exclusively found in the realm of high-energy physics, and in laboratories like the Harvard Cyclotron Lab and the Los Alamos National Laboratory. It was felt by most experts that protons would forever remain an esoteric curiosity, reserved for treatment of only the toughest tumors (like those abutting the spinal cord), and would never be employed in mainstream clinical radiation oncology. One of the few radiation oncologists who refused to accept this “fact” was Dr. James Slater, then chairman of the department of Radiation Medicine at Loma Linda University Medical Center. Dr. Slater believed that the physical superiority of protons could best be demonstrated and exploited if they could be used in a clinical setting like a hospital or, in other words, in the same environment in which x-ray therapy is routinely administered. In the early 1980’s he founded a working group with the Fermi National Accelerator Laboratory and the Argonne National Laboratory which was dedicated to designing and constructing a hospital-based proton beam treatment center[9]. Construction began at Loma Linda in April 1988, and the first patient (a nurse with an ocular melanoma) was treated in October 1990. At the time of its construction the Loma Linda University conformal proton beam treatment center was the single most expensive medical device ever built, at a cost (including research and development) of $120 million. The facility contained four patient treatment rooms and was designed to eventually treat up to 150 patients per day (in contrast, recall that over a ten-year period, only 100-odd prostate patients were treated at the Harvard Cyclotron Laboratory).

Proton Beam Radiation Therapy of Prostate Cancer – The Loma Linda Experience

Conformal proton beam treatment of prostate cancer commenced on October 8th, 1991 and has continued uninterrupted since that date. The primary goals of therapy have been to improve local disease control (via dose-escalation) while simultaneously limiting treatment-related side effects to an acceptable level. Currently, a “typical” treatment course for early-stage prostate cancer (T1b-T2b disease) is to irradiate the prostate to a total radiation dose of between 79-81 Gy (=7,900-8,100 rads), with treatment taking place daily, five days per week, over a period of nine weeks. Precision therapy requires a reproducible patient position, so the first phase of each patient’s treatment planning process consists of the construction of a customized full-body immobilization device, or “pod,” which is in effect a Styrofoam and fiberglass shell that conforms to the patient’s body contours and ensures a stable frame of reference for daily treatment. Before the CT planning scan, and before each day’s treatment, a water balloon is inserted into the rectum and inflated with 120ml of water. This serves to minimize prostate motion by pushing the gland anterioaly against the pubic bone and also displaces the majority of the rectum from the proton radiation field, protecting this vital organ by reducing the volume of rectal tissue which receives any radiation dose. A thin slice CT planning scan of the pelvis is performed to create in effect a 3-dimensional model of the patient’s pelvic anatomy. This data is critical in designing the patient-specific devices which attenuate the proton beam so that it delivers its maximal radiation dose within, and not outside of, the prostate.

On treatment days, the patient arrives at the facility and changes into the inevitable gown. His pod is retrieved from a storage area and locked to the treatment table. The patient is placed in his pod and the rectal balloon is inserted and inflated. Correct patient position is then checked daily by obtaining two low-power orthogonal (at 90 degree angles to each other) x-rays; the images are captured by a digital imaging device and compared (via computer) to similar images created at the time of treatment planning. The “difference” between the daily position (if any) and the “ideal” position is adjusted by moving the treatment couch in the appropriate directions, the therapy personnel leave the room, and treatment is delivered. Prostate patients are typically treated in fifteen minute time slots, with the majority of that time being utilized to verify correct daily positioning.

In general, treatment is well tolerated. There are no physical restrictions placed on the patient during treatment and, in fact, exercise is encouraged. Common side effects include feelings of urinary frequency and urgency; these symptoms commence during the first two weeks of treatment and are usually of the “annoyance” variety. If necessary, they can be managed with over-the-counter medications like ibuprofen. Since, unlike x-ray therapy, the small intestine is not irradiated, diarrhea is not typically an issue and in fact constipation (from the rectal balloon in-
sertions) is a relatively common occurrence. During the last few weeks of treatment it is also common to notice some redness of the skin over the proton beam entrance path; this is due to the slight amount of radiation dose deposited in the skin as the protons enter the body.

Following the completion of treatment, patients are followed via methods identical to those employed in x-ray therapy and surgery i.e., regular PSA determinations and physical examinations, with additional tests (bone scan, re-biopsy, etc.) being obtained should circumstances warrant. Treatment-related side effects are scored using the Radiation Therapy Oncology Group’s (RTOG) morbidity scoring system, with data on side effects being gathered from patient interviews, patient-completed questionnaires, and review of outside records.

Results of treatment have been published in numerous peer-reviewed medical journals. Currently, the most comprehensive review of long-term results from Loma Linda was published in the International Journal of Radiation Oncology, Biology, and Physics in 2004. This paper focused on 1,256 patients with stages T1-T3 prostate cancer, all of whom were treated between October 1991 and December 1997, and none of whom received any adjuvant hormonal therapy. The radiation dose employed was 74-75 Gy (our institutional standard at the time, based on the Harvard experience), and the median follow-up was sixty-three months. Biochemical disease-free survival (as defined by PSA-based criteria) was 95% in patients with pre-treatment PSA’s of < 4.1, 85% for PSA of 4.1-10.0, 65% for PSA of 10.1-20.0, and 48% for PSA’s of 20.1-50.0. These numbers compare favorably with a similar group of patients (stratified by pre-treatment PSA, Gleason Score, and clinical stage) who underwent radical prostatectomy at Johns Hopkins[10]. The five and ten year incidence of moderate to severe Genitourinary and Gastrointestinal morbidity was 1%. This series represents one of the largest groups of individuals treated with a three-dimensional conformal proton beam technique treated at the same institution and demonstrates that the treatment is well tolerated and capable of producing biochemical disease-free survival rates equivalent to those achieved with other treatment methods[11].

The PROG-9509 Randomized Trial
One of the bedrock tenants of radiation oncology is that increasing the radiation dose to a tumor will increase the probability of sterilizing the tumor and, hence (if the disease has not already metastasized) the probability of cure. It will be recalled that the original Harvard randomized trial demonstrated that those patients who received the higher radiation dose were less likely to experience progression of disease within the prostate gland. Because of the advanced stage of the patients in the Harvard trial, improving local control did not equate to improved cure, but the data suggested that if dose-escalation was performed in patients who had early stage disease and hence a low chance of having already developed metastasis, those patients receiving a higher dose may be more likely to be cured.

It was to test just this hypothesis that in 1996 physicians at Loma Linda University and Harvard instituted a prospective, randomized trial, known as the PROG (for Proton Radiation Oncology Group) 9509 trial. Patients enrolling in this trial were randomly assigned to receive a total radiation dose of either 70.2 or 79.2 Gy, with the former dose chosen to represent the “standard” radiation dose then prevailing in radiation oncology. Between 1996 and 2000, some 393 patients were enrolled and have been followed continuously ever since. PROG 9509 was the first multi-institution prospective randomized trial of dose escalation ever performed in prostate cancer, and its success is a tribute to those brave and generous patients who were willing to participate in a clinical study.

The results of the PROG 9509 trial were published in the Journal of the American Medical Association in 2005[12]. The data strongly confirms the hypothesis that dose-escalation reduces biochemical failure (rising PSA, which is a surrogate for disease recurrence) in early stage disease. The advantage of dose-escalation was seen amongst all patient subgroups and was strongly statistically significant. It equates to an approximately 20-30% reduced risk of biochemical failure at five years in the high-dose group, and it is highly likely that this difference between groups will increase with further follow-up. Equally importantly, the increase in radiation dose was not associated with an increase in moderate to severe treatment related morbidity - in fact, the incidence of moderate or greater long term side effects was <1% in both groups. As a consequence of this trial, the new “standard” radiation dose for early stage disease at LLUMC and the other proton centers is now equal to...
the “high dose” arm of the 9509 trial, and a further
dose-escalation study (to 82 Gy) has recently been completed.

**Protons VS IMRT**

One of the most recent technological advances in x-ray therapy has been the development of Intensity Modulated Radiation Therapy (IMRT). In IMRT, a computer-controlled linear accelerator is used to treat a tumor, like prostate cancer, with a multitude (the typical plan utilizes seven to fourteen beams) of individually shaped x-ray beams. In order to protect normal tissue, the intensity of the beams is adjusted dynamically by placing within the beam an absorbing material (typically made of Tungsten or some other high-density metal) so that when a particular beam path traverses large amounts of normal tissue the beam intensity is decreased. This type of treatment will produce a high-dose region which nicely surrounds the prostate but (and this is an important point regarding the difference between proton therapy and IMRT treatment) at the expense of increasing the amount of normal tissue which receives low to moderate radiation doses. The reason for this gets back to the aforementioned physical differences between protons and x-rays. IMRT is still fundamentally x-ray based therapy, and while one can change the intensity of the beam, what one cannot do (for it is a physical impossibility to do so) is to get an x-ray beam to stop at some point in space.

Patients and colleagues routinely tell me that IMRT has made protons unnecessary because with IMRT we can achieve high dose distributions that in some cases are similar to those achievable with protons. When I point out that the integral dose (total dose to normal tissue) is 3-5 times less with protons than when IMRT is used, they will often dismiss this low-dose radiation as being unimportant because it is not likely to cause any clinically identifiable problems. I consider this argument flawed because of the following points:

1. Virtually every advance in radiation treatment technology since the inception of radiation therapy has been directed at the goal of reducing any radiation dose to normal tissue to the greatest extent technologically possible. IMRT reverses this trend because it exposes large amounts of normal tissue to low-dose radiation.

2. Our knowledge of radiation-induced organ injury is based primarily on analyzing the volume of that organ which receives a high radiation dose. Our understanding of the effect of treating a large volume of a normal organ to a low dose is very limited, and the long term effects of such exposure are poorly understood.

3. The only absolutely safe dose of radiation that we know of is zero. Therefore, anything we can do technologically to limit as much normal tissue to zero dose will always be desirable and advantageous to the patient.

Conformal proton beam radiation represents the future of external beam radiation therapy. In terms of technological development it is presently in what I would consider to be the first generation of development. As accelerator technology matures, and active scanned proton beams become a reality (this latter development is nearing its introduction into clinical oncology and is already available at one center in Europe) the disparity between what can be achieved with protons and what one must accept with x-rays (including IMRT) will only become greater[13-15].

**The Future**

Conformal proton beam radiation therapy of prostate cancer is now available at five institutions in the United States (Loma Linda, Harvard, MD Anderson Cancer Center, University of Florida, Indiana University) with several other facilities either under construction or in the planning stages. Ongoing clinical research will focus primarily on further dose-escalation and on a concept known as hypofractionation, in which higher than “standard” daily radiation doses are given so as to deliver the same equivalent total radiation dose to the prostate over, say three to four weeks as would typically be given over nine weeks. Another concept under active investigation is that of intra-prostatic boosting, in which areas within the prostate gland containing identifiable tumor (as delineated by endo-rectal MRI or PET) will receive even higher doses of radiation than the remainder of the gland.

**Conclusion**

Conformal proton beam radiation therapy of prostate cancer is safe and effective, and can produce biochemical disease-free survivals which are comparable to other treatment methods. The physical characteristics of protons guarantee that for any given treatment
plan they will always result in a lower total radiation dose to normal tissue than can be achieved with any form of x-ray therapy, which over a century’s worth of clinical experience in radiation oncology has been shown to always be beneficial to the patient. This technology continues to evolve and impending advances in proton beam treatment delivery will serve to further improve our ability to irradiate the prostate to high doses while simultaneously minimizing normal tissue toxicity.


WHAT THE HECK HAS BEEN GOING ON IN MY WORLD-PART 14!!!

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(Note: You can now log on to www.seminarsprevaltmed.com to get info on the medical journal edited by me-shameless plug #4309)

Let me see if I get this straight. Michigan loses to Ohio State on a controversial call (for those of you who missed it, there was a helmet hit by Shawn Cra-

ble from Michigan on Troy Smith from Ohio State and I believe Mr. Smith got a small boo boo from the hit, so they threw a flag) and gets beat in the Rose Bowl by 2 touchdowns from that school out West where the players apparently get cold hard cash for playing on the team (am I bitter about this game or what). Also, just when you think it could not get any worse, Ohio State gets the Astroturf kicked out of them by Florida in the National Championship Game (no, I do not need my cranium examined, I may hate Ohio State when they play Michigan but otherwise I am always the Big Ten fan - all the way baby)! These are dark days my friends. I know that you are thinking that these are only football games and not life or death, but this does not help my pain, which is so bad! How bad is my pain? It hurts more than a 7-foot Urologist with large hands doing a rectal exam with the entire hand - that is how bad it hurt me (rim shot please).

81) Men on androgen deprivation therapy (ADT) for prostate cancer are simply not getting enough calcium and vitamin D in their diet and/or from supplements, and these two supplements alone could protect them potentially from numerous serious side effects.


This was a nice lifestyle study from Barcelona, Spain. A total of 372 prostate cancer patients treated by surgery (106 patients) or taking androgen deprivation therapy (ADT, 266 patients) were a part of this study. Daily calcium intake was calculated after a dietary interview was completed at the time of bone mineral density (BMD) screening with a Dual-Energy X-ray Absorptiometry (DEXA) at the lumbar spine and hip. DEXA is the gold standard for diagnosing osteoporosis in the U.S. and most other countries in women and men. The median age of this group was approximately 70 years old, the average Gleason score was between 6 and 7 (6.8), and the average PSA at diagnosis was 9.8 ng/ml and 75.1 at the time of the beginning of ADT. Out of all of these men the following DEXA results indicated:

-183 men had osteoporosis
-132 men had osteopenia
-57 men had a normal bone mineral density (BMD)

The usual recommendation, at least minimally for men this age, is to get 1,000 mg of calcium per day,