TRANSPERINEAL PROSTATE RADIATION SEED IMPLANTATION

Recent clinical treatments indicate that transperineal seed implantation provides an accurate and direct method of curing localized prostate carcinoma while protecting normal surrounding tissue of the bladder and rectum from high doses of radiation. Gil Lederman, M.D. responds to questions posed by Dr. Stanley H. Kornhauser regarding this noninvasive and highly successful treatment modality.

Gil Lederman, M.D. and Stanley H. Kornhauser, Ph.D.

Dr. Kornhauser/Question 1: Why is there growing interest in the treatment of localized prostate cancer?

Dr. Lederman: Only prostate cancer that is localized is potentially curable. Two developments have revolutionized prostate cancer - the first diagnostic and the second therapeutic. Blood testing has been implemented using the Prostatic Specific Antigen (P.S.A.). This has encouraged men to seek annual screening, much like women have done with mammography and PAP smears. In the past, the majority of men diagnosed with prostate cancer had metastatic disease - cancer that had left the prostate and traveled most commonly to the bones, which is an incurable situation. Today, the majority of men diagnosed have localized disease, thanks in large measure to effective screening. The second development is new treatment modalities such as transperineal radiation seed implantation -- i.e., radioactive seeds placed directly into the prostate, avoiding open surgery and its known limitations.

Dr. Kornhauser/Question 2: How reliable is the P.S.A. for diagnosis of prostate cancer?

Dr. Lederman: Elevated P.S.A. may be observed in men with no cancer, but with only benign enlargement of the prostate. Similarly, infections or manipulation of the urinary tract may elevate P.S.A. The elevation of P.S.A. associated with infection should be re-evaluated after antibiotics are prescribed. Similarly, P.S.A. should fall after time in relationship to the manipulation. Benign enlargement of the prostate is best evaluated with a biopsy to distinguish it from malignant disease.

Dr. Kornhauser/Question 3: What is the likelihood of a man having an elevated P.S.A.?

Dr. Lederman: Recent data by Catalona, et al. shows that of more than 10,000 men undergoing P.S.A. testing, 90% were in the normal range, 8% in the intermediate range, and 2% in the high range.

Dr. Kornhauser/Question 4: What is the likelihood of having prostate cancer it the P.S.A. is in the intermediate range?

Dr. Lederman: If one defines the intermediate range as 4.1 to 9.9 ng/cc, one-quarter of the men will have prostate cancer. The interesting point is that the cancer is confined to the prostate in 99% of the men in this category. That is, it is localized and still potentially curable.

Dr. Kornhauser/Question 6: Can one rely on the P.S.A. for diagnosis of prostate cancer?

Dr. Lederman: Absolutely not. Some men with benign disease will have an elevation of the P.S.A., and approximately one-quarter of the men with localized prostate cancer will have a normal P.S.A. test. Therefore, P.S.A. testing by itself is not a "gold standard" diagnostic measure.

It must be in the context of the physical exam and biopsy results. CT scans of the pelvis and abdomen as well as bone scans are also performed to help confirm the localized-only nature of the prostate cancer. If metastatic disease is found, then appropriate therapy is prescribed.

Dr. Kornhauser/Question 6: Does the likelihood of cancer rise as the P.S.A. measurement climbs?

Dr. Lederman: When the P.S.A. is greater than 10 ng/cc, 60% of the men have cancer. One-half will have localized disease, as noted by Catalona, et al.

Dr. Kornhauser/Question 7: How does routine screening help?

Dr. Lederman: Less advanced cancer is seen in men who undergo routine P.S.A. testing than in whom only an abnormal rectal exam produces the diagnosis. That means that blood testing along with physical exam is much more sensitive than physical exam only to detect early disease. The benefit for the man with early disease is that the likelihood of cure is proportionally much higher and options for therapy are greater, as well.

Dr. Kornhauser/Question 8: May a man with a normal prostate by a physical exam still have prostate cancer?

Dr. Lederman: Yes. A significant number of men with normal-feeling prostates will have an elevation of the P.S.A. Without the P.S.A. test, about one-half the cancers would be missed by the physician's physical exam only. These men have the greatest likelihood of disease-free survival because of potential early diagnosis.

Dr. Kornhauser/Question 9: How does the P.S.A. influence knowledge about the need for biopsy?

Dr. Lederman: Recent data shows that if the prostate is suspicious only, 12% of men biopsied have cancer. However, if the P.S.A. is elevated only, then 24% of the men evaluated have cancer. When both the P.S.A. was elevated and suspicious findings were noted on rectal exam, more than one-half the men had biopsy-proven prostate cancer. Thus, the rationale for early detection is strong. Hand-in-hand with early detection are new diagnostic treatments.

Dr. Kornhauser/Question 10: What are the treatment options available for men with prostate cancer?

Dr. Lederman: This depends upon the extent (the stage) of the disease. If the prostate cancer is metastatic, having spread to distant sites, treatment options are available but are more limited than for localized disease. For men with metastatic prostate carcinoma to bones, the standard treatment is hormonal manipulation using medication such as Lupron and Flutamide to suppress the activity of the cancel. This will produce a therapeutic effect in the majority of men. The problem is the limited usefulness of the agents. Second-line hormonal therapy is much less beneficial and is unlikely to produce a favorable effect for most men.

Dr. Kornhauser/Question 11: How long do hormonal agents work for localized diseases?

Dr. Lederman: Like with metastatic disease, hormonal agents only work transiently. Furthermore, they do not cure any man of prostate cancer, so their potential use in limited stage disease is modest.

Dr. Kornhauser/Question 12: What is the role of hormonal agents in localized prostate cancer?

Dr. Lederman: In our hands, we use hormonal therapy to diminish the size of the enlarged prostate in order to make the cancer more amenable to aggressive local regional therapy.

Dr. Kornhauser/Question 13: What are the options available to the man with localized prostate cancer?

Dr. Lederman: The man is generally told there are a variety of options available. For the older man with co-morbid disease who has non-aggressive cancer, observation might be recommended. Studies attempting cost containment are certainly looking at this option. The problem is for the man who is otherwise in relatively good health. Observation means no treatment and no treatment means a great gamble for that man - a gamble that he will die of something else first.

Dr. Kornhauser/Question 14: Is there any other kind of cancer that is being observed only?

Dr. Lederman: No. Any other localized cancer in the body is treated with the expectation of a cure. Our patients are highly motivated and enthusiastically seek aggressive therapy in order to be cured.

Dr. Kornhauser/Question 15: What are the other treatment options available?

Dr. Lederman: Potentially curative therapies include radical surgery, standard external beam radiation, transperineal radiation seed implantation, or cryotherapy.

Dr. Kornhauser/Question 16: What are the benefits and limitations of these techniques?

Dr. Lederman: Radical surgery has been used for many decades. It has a known track record. Its success, as well as its failures, are well charted. The vast majority of men undergoing radical prostatectomy will have no further sexual potency and 5% to 10% of men will have urinary incontinence. This urinary incontinence may be anything from constant leakage of urine to dripping of urine with coughing, laughing or other physical activity.

A lesser surgical procedure, called nervesparing, is being performed in order to maintain sexual function. The fear is leaving cancer cells behind after this open, radical procedure. I believe if men want to preserve sexual function and still undergo aggressive treatment, then the transperineal seed implant approach merits strong consideration.

The benefits of surgery are that a percentage of men are cured and urologic surgeons often consider surgery as the "gold standard."

A significant proportion of men undergoing radical prostatectomy have cancer cells left behind. That is, a surgeon has cut through the cancer, unable to fully resect it. Those men pay the price in surgical morbidity and mortality and yet do not derive the benefit of total removal. Cancer cells left behind mean cancer cells left to grow.

Furthermore, surgery is a radical procedure with a known morbidity and mortality associated with the procedure, as well as a generally prolonged convalescence period.

Dr. Kornhauser/Question 17: And standard external-beam radiation?

Dr. Lederman: Most in the field believe standard external-beam radiation is equal in effectiveness to radical prostatectomy in curing men of prostate cancer. All radiation is limited by the surrounding structures. In the front of the prostate is the bladder and behind is the rectum. Standard radiation must penetrate the bladder and rectum to attack the prostate cancer, but the normal surrounding tissues limit the radiation dose. Routinely, about 7,000 rad has been given to the prostate, and some dose escalation studies are now trying to take this slightly higher. Even with the dose escalation studies, beams still must travel through normal structures which increases the likelihood of side effects.

Furthermore, the prostate is a gland that moves. We have watched it change position with gas or feces within the rectum, changing amounts of urine in the bladder, respiration, and patient motion.

If small external radiation fields are going to be used to very high doses, then normal surrounding tissues are at risk. That the prostate is moving makes it a target that is difficult to hit by external-beam techniques only. That is why we have a different, more aggressive, more precise approach.

Dr. Kornhauser/Question 18: Describe the rationale of transperineal radiation seed implantation.

Dr. Lederman: The transperineal seed implantation allows us to directly place the radiation seeds into the prostate gland using predetermined computer planning guided by sophisticated fluoroscopy and transrectal ultrasound imaging of the prostate. This means the man undergoing radiation seed implantation can have the seeds placed directly into the prostate gland, being pushed through the skin, avoiding any incision or major open operation. Shortly thereafter he returns to quite normal function. Using radiation seeds placed directly into the prostate cancer, the radiation does not have to travel through the bladder and rectum to get to the prostate.

Dr. Kornhauser/Question 19: What are the advantages of this technique?

Dr. Lederman: Using radioactive iodine seeds, the majority of the prostate gland receives 18,000 rad and the entire prostate receives more than 12,000 rad. Furthermore, in our technique, radiation seed implantation is teamed together with external-beam radiation to give a homogeneous dose to the prostate and the surrounding tissues. Thus, for the man receiving iodine seed implantation and external-beam radiation therapy, more than 20,000 rad is given to the central prostate and at least 16,000 rad to the periphery of the cancer. While the external-beam radiation is given, the seeds are still active. Thus, the biologic effect is greater than when administered in the reverse sequence.

Dr. Kornhauser/Question 20: Is radiation dose that important in treating prostate cancer?

Dr. Lederman: Most radiation oncologists believe that there is a dose response curve - the higher the dose, the more likely the cancer will be cured. However, by using external-beam techniques only, the dose has been markedly limited by the normal surrounding tissues, especially the bladder and rectum.

Dr. Kornhauser/Question 21: How well has your technique been tolerated?

Dr. Lederman: We have treated hundreds of men using the transperineal radiation seed implantation and external-beam technique at Staten Island University Hospital. All men undergoing radiation for prostate cancer will have a change in bowel and bladder function. This is most pronounced during the course of radiation, then returns toward normal. Most have increased frequency of bowel and bladder function with some irritation. About 15% of men will have some blood - either on the toilet paper or in the toilet - during the course of radiation and in our experience, this is transient.

One percent of men have required blood transfusions and no patient has required any open surgical procedure due to radiation effects.

Dr. Kornhauser/Question 22: What about sexual function?

Dr. Lederman: The majority of men sexually functional before our program remain sexually functional after treatment. Obviously, sexual function diminishes with age, and some men undergoing treatment already have some diminishment of these abilities.

Dr. Kornhauser/Question 23: How successful is transperineal radiation seed implantation?

Dr. Lederman: The vast majority of men are entering remission, as defined by normalization of P.S.A. and normal physical exam. We are presently compiling data using biopsy results one year after treatment to confirm the above.

Dr. Kornhauser/Question 24: Do all men get the two-pronged approach for localized prostate cancer?

Dr. Lederman: Yes. We treat all men with localized prostate carcinoma using prostate seed implantation and external-beam radiation. Prostate seed implantation is conducted to give high doses of radiation directly to the prostate while the external-beam radiation treats the prostate and surrounding tissues, including the lymph nodes. This five-week course of external-beam radiation therapy has been the backbone of standard therapy used over decades, and we believe it is beneficial to use it to attempt to eradicate microscopic cells that might have escaped the prostate and have not been detected by other means, but are still amenable to such therapy.

The five-week course of external-beam radiation therapy has been used for decades and we do not seek to discard medical knowledge. Rather, we use it to enhance the potential curative possibilities of these seed implantations of the prostate.

Dr. Kornhauser/Question 25: Have other centers confirmed your data?

Dr. Lederman: Yes. Blasko, et al. have shown that 96% of men have no confirmed cancer when biopsy is performed one to three years after diagnosis. Furthermore, the vast majority of men - 90% - are alive and free of disease.

Dr. Kornhauser/Question 28: How does this compare to similar surgical or standard radiation techniques?

Dr. Lederman: The Blasko group compared its 90% success rate at 37 months of follow-up to a group undergoing radical surgical procedure having only a 75% success rate at 24 months (Oesterling, et al.). Obviously, one would expect the surgical group to have a less than 75% success rate when its data reaches 37 months maturity. This would suggest a dramatic benefit using the radiation techniques. Similarly, Walsh, et al. at Johns Hopkins noted a 76% success rate at 48 months.

Dr. Kornhauser/Question 27: Is, obtaining 10 or 15 years follow-up data crucial for treatment of prostate cancer?

Dr. Lederman: It is always desirable to have a track record of technology. However, our program is not diminishing treatments; we believe it is only enhancing therapy. The backbone - the five week course of radiation delivering 4,500 rad -- is still present. Only the boost dose to the

prostate gland has been altered dramatically upward to increase the radiation dose and thereby enhance effectiveness.

Dr. Kornhauser/Question 28: Why do you believe the success rate using seed implantation appears greater than with surgery?

Dr. Lederman: Surgery's goal is limited only to the removal of the prostate. Furthermore, some men don't make it through the surgical period. Our technique has no acute morbidity and treats a larger area than what the surgeons attempt.

Dr. Kornhauser/Question 29: Has radiation seed implantation data been compared to standard radiation data using external beam only?

Dr. Lederman: Yes, retrospectively. There is an improvement in disease-free survival using the transperineal radiation seed technique.

Dr. Kornhauser/Question 30: What different types of isotopes are used for prostate seed implantation?

Dr. Lederman: We use palladium and iodine seeds. Iodine has a half-life of 60 days and palladium has a half-life of 17 days. Using palladium seeds, the radiation dose is administered over a shorter period of time and therefore has a greater biologic effect on the cancer.

Dr. Kornhauser/Question 31: Why isn't palladium used on all patients?

Dr. Lederman: Because of its greater dose rate, it also has more irritative effects on the bladder and rectum. Therefore, it is used only in specific instances.

Dr. Kornhauser/Question 32: When do you use palladium seed implantation?

Dr. Lederman: Our data has revealed excellent results (100% control rate) in men with Gleasons score 8, 9 and 10 pathologic rate of prostate cancer.

Similarly, men with aneuploid cells and a Gleasons score of 5, 6 and 7 have also revealed excellent results. For men with a lower Gleasons score or intermediate Gleasons score but with diploid cells, iodine is used.

Dr. Kornhauser/Question 33: What is "Gleasons score?"

Dr. Lederman: Gleason devised a system to look at two separate areas of the malignancy and grade them individually, then add up the results to produce a score. A grade of 1 to 5 is entered with "l" being the most well differentiated and "5" being the least differentiated. These two areas are added to produce the score. The score can be anywhere from 1 + 1 = 2 Gleasons score, all the way to the worst pathology, 5 + 5 = 10 Gleasons score. Prognostically, men with scores closest to "2" have done the best, though with our techniques, men with a high Gleasons score that are treated aggressively are doing exceedingly well.

Dr. Kornhauser/Question 34: What are aneuploid cells?

Dr. Lederman: Aneuploid cells are cancer cells having an abnormal number of chromosomes. Cancer cells that are aneuploid tend to be more aggressive and have a worse outcome. It is for that reason that we use palladium seeds and have, thus far, shown superb clinical outcomes.

Dr. Kornhauser/Question 36: What have been the patients reactions to this technique?

Dr. Lederman: The treatment is generally well-tolerated. Unlike chemotherapy, there are no injections, lowering of the blood count, nausea, vomiting, or hair loss. The vast majority of our patients remain active, at work and at home. We have treated everyone from toll collectors on the interstate to businessmen running $100 million-a-year international companies. Furthermore, many men remain sexually active during this course of treatment. Of course, there will be frequent trips to the bathroom, increased urgency in urination, and irritation that diminishes with time.

Dr. Kornhauser/Question 36: How difficult is the transperineal radiation seed implantation procedures?

Dr. Lederman: For the patient it is very simple. We often do it under spinal anesthesia so the patient is awake during the procedure. For those who desire to be asleep, either sedation or general anesthesia can be used.

Dr. Kornhauser/Question 37: And for the physician?

Dr. Lederman: The physicianÌs role is part of a team. The procedure here is headed by Dr. Peter Albert and Dr. Adley Raboy, Director and Associate Director of Urology at Staten Island University Hospital, and by myself in Radiation Oncology. There is a group of medical physicists including Dr. Harunor Rashid, Dr. Guo-Xin Qian and medical dosimetrists Mike Fastaia and Tom Constantino. Dedicated anesthesiologists in the operating room, as well as urology nurse specialist Susan Smith, oversee the actual implantation of seeds.

Dr. Kornhauser/Question 38: Can the external-beam radiation treatments be performed anywhere?

Dr. Lederman: Essentially all men are treated on the Varian 2100C Linear Accelerator using the 18MV beam. Furthermore, the beams are specially weighted heavily from the lateral fields to help further protect the bladder and rectum. Additionally, unique lead blocks are placed into the linear accelerator to protect the bladder and rectum. Thus, we take special precautions that are not standard because of the high radiation doses being used. Field sizes of the radiation beams are specially devised for each patient depending on the prostate size and the position of the normal structures.

Dr. Kornhauser/Question 39: How are the patients aligned for their daily treatments and how is accuracy confirmed?

Dr. Lederman: Patients are aligned using a variety of techniques including special optimeters in the linear accelerator to determine the distance from the source of the beam to the patient. Lasers are used to accurately position each patient daily, as well as field lights indicating the exact size of the radiation field on the patient. Beam films confirm the accuracy of the beam in comparison to the initially planned treatment field which is performed on a dedicated simulator.

Most of our patients today use body radiosurgery. They like this approach because of the greater accuracy. Body radiosurgery allows for stereotactic external frame with fiducials (markers) that are seen when the patient undergoes scanning. A custom-made mold is produced for each patient that fits inside the frame. Then the patient is scanned and the organs are computerized. Radiation beams come from a variety of different angles to attack the cancer and to try and avoid healthy, normal tissues.

In comparison to standard radiation, there is a smaller field of radiation that is more accurate and, therefore, should be few side effects. Our data compared to conformal radiation shows benefit, with more men cancer-free in our hands.

Dr. Kornhauser/Question 40: Please describe this simulator?

Dr. Lederman: A radiation simulator is a machine which takes high quality x-rays and allows us to outline exactly where the prostate is located. On the simulation day, a catheter is introduced into the bladder and a small tube into the rectum to position contrast material. With the outline of the bladder and rectum present, the prostate's position can be accurately determined and the normal tissues detected. The bladder and rectal tube are removed after 45 minutes and there is no need to place them again.

Dr. Kornhauser/Question 41: How do you follow men who have gone through your treatment plan?

Dr. Lederman: Men are scheduled for prostate evaluation, and in fact a complete physical examination, six weeks after treatment and then twice a year. Routine P.S.A. testing is done at this time.

Dr. Kornhauser/Question 42: Are lymph nodes ever evaluated for involvement by the cancer?

Dr. Lederman: Doctors have developed an extraperitoneal endoscopic technique to evaluate pelvic lymph nodes. This avoids radical open procedure and is well tolerated by the patients. This gives prognostic information in select patients.

Dr. Kornhauser/Question 43: Who is a candidate for this endoscopic lymph node technique?

Dr. Lederman: Patients who are at risk for lymph node involvement, meaning large prostate, high Gleasons score and marked elevation of P.S.A.

Dr. Kornhauser/Question 44: What technology is "down the road" for men with localized prostate carcinoma?

Dr. Lederman: We obviously are very pleased with the beneficial effects of the radiation seed implantation program. A similar approach using cryotherapy is being developed by Drs. Raboy and Albert, who treat those with refractory localized disease.

Addendum:

Since this article, there has been a tremendous evolution in technology and data. While early ultrasound machines were revolutionary at the time, the ongoing computer age has produced better images, which results in better quality implants. The high-resolution machine sees the prostate and surrounding tissues. Furthermore, we have used fluoroscopy originally and throughout the years. Better quality camera and radiation protection for the patient and physician means more imaging and higher quality imaging. In the early years, computerized pre-planning was used. That meant the plan was made outside the operating room – often days or weeks before and then the plan was transferred to the operating room. Nowadays, we routinely use intraoperative computers to help direct each seed and know the dose at the time of the implantation.

In the early years, Iodine seeds (having a half-life of 60days) were mainly used. Nowadays, we use Palladium seeds almost exclusively because the Palladium seeds have a shorter half-life and seemingly higher cancer-free survival at ten years.

PSA (rostratic Specific Antigen) screening is still critical. In the early years, only men with nodules or elevated PSA's were biopsied on a regular basis. Some studies have shown that even biopsing men with PSA's below 4 can have a significant effect on the discovery of prostate cancer. Some studies have shown that routinely biopsing men with PSA's 2-1/2 to 4 has about a 20% likelihood of finding cancer.

In the early years of PSA screening, the incidence of prostate cancer rose greatly. Subsequently, the number of diagnosed cases per year fell off probably because the testing made up for many lost years. In earlier years, many men were diagnosed with prostate cancer once it had spread to the bones. PSA has revolutionized that so that most men are diagnosed when the cancer is confined and most likely curable.

Treatments are vast. What is different today, however, is that their long-term data for prostate brachytherapy and this long-term data in our hands show advantage to seed therapy and body radiosurgery compared to radical therapy. We also have benefit compared to other forms of radiation.

Our current data does not show benefit to short-term hormonal use. Men who receive hormonal therapy (hormones essentially block the production of testosterone) do have side effects such as hot flashes, weight gain and sometimes breast enlargement as well as loss of libido and erections. Men generally do not like hormonal therapy. Again, our data does not show survival benefit for short-term use There are some other studies showing years of hormonal therapy my be advantageous when added to conventional radiation.

It should be noted that radiation doses are different with Iodine and Palladium because of the duration of the radiation exposure. Palladium usually has a lower prescribed dose. This does not mean the effectiveness is less – in fact, essentially every study shows they are nearly equivalent although currently our studies at ten years seem to show an edge to Palladium.

Free seminars are open to the public, to meet our physicians in an informal setting. We also have a hot line at 212-CHOICES and also questions can be e-mailed to gil.lederman@rsny.org. We believe that each man should investigate all treatment options before proceeding with cancer treatment.