

Seed Implant Radiation Therapy

LDR (low dose rate) brachytherapy for prostate cancer is more commonly known as seed implants. You may be familiar with this treatment option but for those of you who may be new to the confusing world of prostate cancer treatment, seed implants involve the insertion of small radioactive pellets or seeds into the prostate by transrectal ultrasound guidance, in order to deliver a focused dose of radiation to the prostate.

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The seeds contain one of three possible radioactive isotopes: Palladium-103, Iodine-125 or Cesium-137. These isotopes have slightly different characteristics, but all are proven effective in eradicating cancer. What they have in common is that they emit low energy radiation for a period of a few months and then become inert. As a result of the low but continuous energy, an intense total dose of radiation is delivered to the prostate, but very little radiation reaches the sensitive surrounding organs such as the bladder and rectum. In the world of radiation treatment, a well-done seed implant offers the best of both worlds: a high dose to the prostate, a low dose to normal tissues.

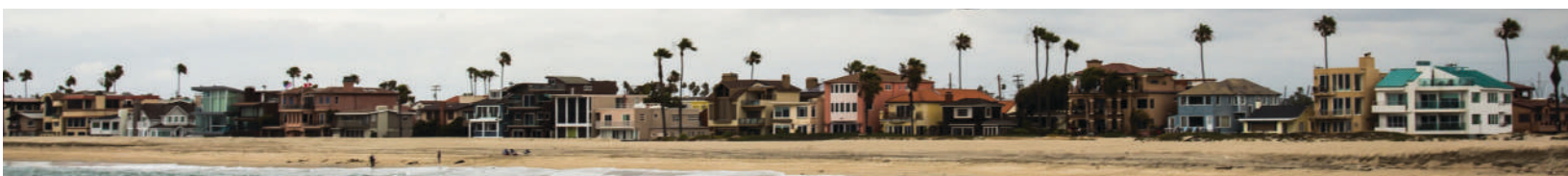
Prostate seed implants have proven to be safe and effective for over 25 years. What

is new about seed implants in 2015? I am excited by a recent study done by Canadian researchers. A major criticism of prostate cancer research is the lack of high quality, prospective, randomized trials that accurately compare the results of various treatments. Well, the Canadians have managed to pull it off. They have just completed analysis of the ASCENDE-RT trial. The results have been presented at several major medical meetings, but have not yet been published and is currently available only in preliminary abstract form.

The ASCENDE-RT trial is a multicenter, randomized trial of dose-escalated external beam radiation therapy versus low-dose-rate brachytherapy for men with unfavorable-risk prostate cancer. 276 men with high-risk disease and 122 with intermediate-risk disease were entered

into the study. All 398 men received 12 months of androgen deprivation therapy (ADT) plus 46 Gy of whole pelvis external beam radiation (EBRT). Then, 200 of the men were randomly assigned to a conformal external beam boost of 32 Gy while 198 were randomly assigned a brachytherapy boost of 115 Gy with Iodine-125.

To put this study in perspective, seed implants historically have been used in one of two ways: 1) as a standalone treatment for low-risk prostate cancer or, 2) as part of combination approach in conjunction with modest doses of external beam radiation for intermediate and high-risk prostate cancer. Many retrospective studies have demonstrated that the combination of modest dose external beam and a seed implant boost with or without hormones is a





Seed Implant Radiation Therapy Continued

very effective treatment. Alternatively, sometimes high-risk disease is treated with hormones plus high-dose external beam radiation (IMRT) without seeds. For years, many radiation experts have contended that while seed boost treatment is effective, the combination of hormones with IMRT is just as effective and is simpler to administer. The ASCENDE-RT is the very first randomized trial ever to evaluate the question of whether adding seed implants improves results to a material degree.

CHARACTERISTICS AND RESULTS OF THE ASCENDE-RT TRIAL

There was a total of 398 men in the trial. The median observation time after radiation for all the men in the trial was 6.5 years, enabling statistical projections to be made for as long as 9 years. Using PSA control rates as the indicator of success, at 5 years 77% of the hormone + IMRT alone were relapse-free compared to 89% of the Hormone + IMRT + seed boost patients. At 9 years, the results were even more dramatic with a relapse free rate of 63% vs. 83% in favor of the seed boost

patients. Thus, 9 years after treatment, the PSA based cure rate of the seed boost patients was improved by 20%!

The other encouraging aspect of this data is the shape of the PSA survival curves. For the seed boost patients, after about 5 years, the curve becomes very flat meaning that very few patients are relapse after 5 years. In contrast, the curve for the IMRT without seed group continues to fall sharply even out at 10 years (patients are continuing to fail). This suggests the likelihood that most of the seed boost patients will continue to remain in remission while the IMRT alone patients may continue to fail.

In summary, this randomized study demonstrates a dramatic 20% improvement in PSA success in patients who received a seed implant boost compared to those who received IMRT alone. The rationale for this improvement is that brachytherapy delivers a higher and more effective dose of radiation to the prostate which is unachievable with external radiation alone.

As you may be aware, there is controversy regarding the importance of PSA-based outcomes. Some physicians feel that a more important endpoint to measure is how many patients are alive and how many died of prostate cancer. How did the ASCENDE-RT trial do with these endpoints? Well, no difference was seen between the seed boost and the EBRT alone groups with regards to overall survival or prostate cancer-specific survival. This finding is no surprise to me and does NOT mean to me that there is no difference in the treatments. This is because not enough follow-up time has elapsed for PSA failures to manifest mortalities. In this era of multiple effective systemic treatment agents, it is not difficult to keep most people from dying of this disease for up to a decade after they have failed primary treatment. It will probably take at least another 6 or 7 years of follow-up for the PSA failures to translate into survival statistics in this study. To get on my soapbox for a minute, PSA is an incredibly important early clinical indication of success or failure. In addition to shortened survival, PSA failure

In 1985, Dr. Blasko and Haakon Ragde, MD, performed the first transperineal, template and ultrasound guided prostate implant in the U.S. Since that time, Dr. Blasko devoted his career to the development, refinement and promotion of this technique. Today, he is internationally recognized as an authority in prostate brachytherapy and is considered one of the founding fathers of this modality. He continues his involvement with brachytherapy by consulting with medical device companies and physicians seeking to improve their brachytherapy skills.

has a very negative impact on quality-of-life. Further diagnostic tests are required, often followed by a lifetime of further treatment with hormones, chemotherapy or radiation. A patient with a PSA failure has a much worse quality-of-life than one who does not.

What else is new in prostate brachytherapy? Brachytherapists continue to analyze and publish excellent 10+ year results for the full spectrum of low to high-risk disease. Numerous comparative quality-of-life studies have appeared demonstrating the favorable side effect profile of brachytherapy compared to surgery or IMRT. But mostly, I am impressed with the continuing evolution of technology and how it has improved the accuracy and reliability of brachytherapy. Transrectal ultrasound imaging has made tremendous strides and I am astounded by the clarity of images I now see compared to the shadows of 10 years ago. We now have the capability of merging and coordinating MR imaging with transrectal ultrasound before, during, and after the operating room for even finer control and knowledge of seed placement. With this faster and more sophisticated computer software, our ability to precisely place seeds and to control the radiation doses to the urethra, bladder, and rectum is greatly improved. I expect these technological improvements to further reduce the chance of complications and further enhance cure rates.

In this era of cost-consciousness, there is an ongoing effort to assess the value of medical interventions by means of comparative effectiveness analysis. This approach uses sophisticated mathematical modeling derived from published outcomes and morbidity data as well as costs to determine the value of one treatment versus another. For low-risk prostate cancer treatment, there have been several comparative effectiveness studies done by the Institute for Clinical and Economic Review (ICER) at Harvard University. Considering outcomes and cost of treatment, the summary of these studies published in 2013 is that brachytherapy for low-risk disease is the most effective and *least expensive* initial treatment compared to IMRT, proton, or surgery.

Given all this very positive news about prostate brachytherapy what is its current status in the United States? Shockingly, there has been a dramatic *decrease* in the use of brachytherapy between 2002 and 2010 (the last year in which data is available). In 2002 brachytherapy was used in 17% of cases but by 2010 it decreased to only 8%. Over the same time interval, surgery increased from 44% to 59%. This shift appears to coincide with the introduction of new technologies such as robotic surgery, IMRT, and proton therapy. The rapid adoption of these very expensive new technologies has occurred despite the absence of randomized prospective data such as the ACENDE-RT data that was presented above. In my



opinion, prostate treatment has migrated away from seed implants, not because of science, but because of economics and politics. All of these new approaches generate much more revenue for both hospitals and physicians. Hospital marketing departments take advantage of seductive terms like “robot-assisted” and “proton” to publically promote their institutions and capture market share. In the final analysis, surgeons like to do surgery and IMRT specialists like to do beam radiation because they get paid more. How interesting is it to note that the popularity of brachytherapy is growing rapidly in many other countries where medical reimbursement is fixed.

Multiple studies over the past 25 years have demonstrated that brachytherapy either alone or in combination with external beam radiation is as effective and—particularly in intermediate and high-risk disease—superior to prostatectomy or IMRT alone for cure potential and quality-of-life. The ACENDE-RT prospective, randomized trial proves the superior cure rates attainable with seed implantation. When these excellent clinical outcomes are coupled with proven cost-effectiveness, what is there not to like about seed implants? ■