Focal Treatment for Prostate Cancer

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Is It Really Necessary to Treat the Whole Gland?

There is a new advance on the horizon for treating prostate cancer that is localized in the prostate gland. It promises to be as effective as whole gland therapy with fewer complications. It is called "focal treatment for prostate cancer".

There will be approximately 240,000 men newly diagnosed with prostate cancer (PCa) this year. The majority of them will have low risk disease. They will be faced with a dilemma: pursue definitive treatment, with its risk of incontinence and impotence or choose active surveillance, with the possibility of missing the window of opportunity for early control or even cure.

Definitive treatment with either surgery or radiation can result in significant changes in a man's long-term quality of life. For example, brachytherapy's late onset complications include a risk of 1-5% gastrointestinal dysfunction, 5-10% genitourinary dysfunction and 30-40% erectile dysfunction (1). Active surveillance is an excellent alternative with far less risk but has been limited by the need for close monitoring with repeated biopsies to monitor for cancer progression. Focal therapy presents a middle ground between definitive whole gland therapy and active surveillance.

Male Lumpectomy

Focal treatment is called "the male lumpectomy." The goal of focal treatment is to treat just the cancer, sparing the rest of the gland and nerves while achieving optimal cancer control and reducing short and long-term changes in quality of life.

Organ preservation, where only the area with cancer is removed, has become a standard for many other types of cancer (breast, lung, stomach, pancreas, rectum, kidney, etc.). For prostate cancer, however, partial gland treatment is not standard. If an individual has 1 core positive in the right apex or 10 cores positive on the right and left sides of the prostate the entire gland is treated in both cases. Limitations in accurately imaging the PCa in the gland and the ability to precisely target and deliver the treatment have prevented focal therapy from becoming a reality. Furthermore, review of prostatectomy specimens demonstrates that prostate cancer is a multifocal process in about 80% of men (2). Given the difficulties with "seeing" the PCa tumor and the fact that many men have multifocal disease has led physicians to treat the entire prostate gland.

These limiting factors that have been hindering focal therapy are now changing. Multi-parametric MRI imaging (MP MRI) has markedly improved our ability to define the prostate's anatomy and identify prostatic disease including PCa within the gland. (3) Also, improved targeted biopsy techniques, fusing ultrasound and MP MRI images together, has defined the PCa lesion more accurately both in location and grade.(4) These improvements mean we can now have a chance to destroy just the cancer, leaving surrounding vital structures intact.

Of course, there are some limitations to this. For example, the MP MRI, is unlikely to miss a Gleason score 8-10 focus of disease, but may miss a small foci of Gleason score 6 disease. Is missing a low risk lesion acceptable? (5)

The concept of the *index* lesion helps explain why missing a small foci of low grade PCa does not preclude focal therapy. One of the strongest arguments against focal therapy is that prostate cancer is a multifocal process. If the other areas of PCa are missed, then only a small group of men who have unifocal disease would be amenable

to focal treatment. The index lesion concept advocates that regardless of whether prostate cancer is multifocal or not, the danger of disease progression is typically driven by the largest/highest grade tumor focus, or "the index lesion"(6). This concept suggests that these smaller lesions are unlikely to be clinically meaningful and can be followed by "active surveillance" while the more deadly lesion is eradicated. It is estimated between 50-60% of men have an index lesion with otherwise small foci of disease that is appropriate for "active surveillance" and focal treatment.

How is Focal Treatment Accomplished?

There are multiple treatment platforms for delivering focal treatment. Each technique utilizes a different type of energy to kill cancer cells. There are thermal approaches that include either cold (cryoablation) or heat (high-intensity frequency ultrasound and laser therapy), and non-thermal approaches that include photodynamic therapy, irreversible electroporation, and radiation.(7)

Cryoablation using small diameter, argon based technology is available and uses localized freezing to kill tumor cells. It is done using ultrasound guidance. The small probe is placed through the perineum directly into the prostate tumor.

HIFU or High Intensity Focused Ultrasound treatment is typically delivered via a transrectal ultrasound probe. In the last issue of Insights, Dr. Laurence Klotz wrote about the development of a trans urethral HIFU delivery system coupled with heat sensing real time MRI to focally ablate PCa.

Laser therapy is performed by inserting an optical fiber into the prostate via a transperineal approach. Once activated, a roughly spherical zone of destruction of about 1 cm in diameter is created over 2-4 minutes.

Photodynamic therapy uses a method where a drug is given intravenously and is taken up by PCa tumor cells. The drug is activated when it is exposed to a specific energy of light. This light is brought to the tumor through special fibers that are placed via a trans peroneal approach.

Irreversible electroporation passes an electrical current through the tumor that creates holes in tumor cells resulting in cell death. This method uses either ultrasound or MRI to direct therapy.

For radiation the most common method used for focal therapy is brachytherapy. This type of treatment uses either radiation seeds (low dose rate brachytherapy) or hollow little tubes where a radiation source runs in and out of the tubes (high dose rate brachytherapy) to precisely deliver radiation directly to the tumor.

There is reasonable clinical experience with cryotherapy, HIFU, and radiation however there is limited data with laser therapy, irreversible electroporation, and photodynamic therapy. It's currently not known whether one of these techniques is advantageous to another. Experience is accumulating with all techniques.

Radiation, however, has the longest follow-up and experience in treating less than the whole gland. The largest study to date investigating focal therapy was recently updated by Nguyen *et al*.(8) 318 patients were treated using intraoperative MRI guidance to deliver low dose rate brachytherapy to the peripheral zone of the prostate only. With a median follow-up of 5.1 years patients with low risk disease had 5 and 8 year PSA control of 96% and 90% (nadir+2 and PSA velocity >0.75 definition of PSA failure). These results are similar to what is expected with whole gland therapy. Focal brachytherapy results at UCLA are preliminary but

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are showing excellent promise in lowering side effects while still treating the index cancer lesion. (9)

Technological advances in delivering different energies to kill localized areas of the prostate with advances are combining within MP MRI and fusion biopsy data to make focal treatment of PCa an attractive adjunct to active surveillance. The annual Montreal Conference on Focal Treatment for Prostate Cancer can be reviewed online to keep abreast of the rapid advances in this field. Our impression is that this type of research and collaboration will confirm focal therapy's effective use in localized prostate cancer and confirm much less morbidity than present whole gland treatment.

References

1. Demanes D, et al. American Brachytherapy Society consensus guidelines for high-dose-rate prostate brachytherapy. Brachytherapy, 2012. (1): p 20-32

2. Tareen B, Sankin A, Godoy G, et al. Appropriate candidates for hemiablative focal therapy are infrequently encountered among men selected for radical prostatectomy in contemporary cohort. Urology, 2009. 73(2): p. 351-4

3. Turkbey B, et al. Multiparametric 3T prostate magnetic resonance imaging to detect cancer: histopathological correlation using prostatectomy specimens processed in customized magnetic resonance imaging based molds. Journal of Urology, 2011. 186(5): p. 1818-24.

4. Sonn G, et al. Value of targeted prostate biopsy using magnetic resonance-ultrasound fusion in men with prior negative biopsy and elevated prostate-specific antigen. European Urology, 2013. March 1,7 E pub.

5. Carter H, Partin A, Wlash P, et al. Gleason score 6 adenocarcinoma: should it be labeled as cancer? Journal of Clinical Oncology, 2012. 30(35): p. 4294-4296.

6. Ahmed H. The index lesion and the origin of prostate cancer. New England Journal of Medicine, 2009. 361(17): p. 1704-1706

7. Coleman J, Sacrdino P. Targeted prostate cancer ablation: energy options. Curr Opin Urol, 2013. 23: p. 123-128

8. Nguyen P, et al. Updated results of magnetic resonance imaging guided partial prostate brachytherapy for favorable risk prostate cancer: implications for focal therapy. The Journal of Urology, 2012. 188(4): p. 1151-1156

9. Kamrava M, et al. Focal high-dose-rate brachytherapy: a dosimetric comparison of hemi-gland versus conventional whole-gland treatment. Brachytherapy, 2013. Feb 11, E pub.