# Why Focal Therapies Won't Work

**Michael Dattoli, MD**

New prostate cancer treatment theories, therapies and approaches seem to surface every month or so these days. It is a challenge for me to keep up with them all. What must it be like for patients, especially newly diagnosed men?

One idea that I am very clear and passionate about is the expanding and even potentially dangerous approach suggesting that newly diagnosed prostate cancer may be defeated by some variety of focal treatment. "Focal" therapies are those that isolate a specific tumor site and direct treatment only to that area and occasionally to other select areas.

Focal therapy sounds pretty straight-forward. After all, we are aware of select tumors of the skin, kidney, extremities (sarcomas) and low-lying ano-rectal cancers that have been treated with organ-sparing focal therapies, often resulting in equivalent rates of cancer control, lower morbidity rates, and less disfigurement. Transferring this experience to other sites, e.g. head and neck, esophagus, stomach, bladder and especially the prostate gland, however, is an ill-advised leap of faith.

The term "field effect" or "field cancerization" has been well characterized in cancer medicine dating back to the 1950's with countless studies focusing on prostate and breast (Cancer, Vol 16, No 5, 1953). In essence it suggests that if a cancer has occurred in one site of an organ, other sites of the same organ are at equal risk for developing cancer.

One only needs to look at breast cancer where focal "lumpectomy" has consistently been found to be inferior to lumpectomy followed by whole breast irradiation, or mastectomy. (NSABP B-06, Clinical Med Res, Vol 1(4), 2003; 20 Year Follow-up of Randomized Trial, NEJM, 347, 2002).

Prostate cancer is <u>rarely</u> a unifocal disease. It is very complicated. Studies have shown the 86% of men with a unilateral (left or right lobe) diagnosis will

actually have bilobar disease following prostatectomy. (Journal of Clinical Oncology, Vol. 32, No. 13, May 2014).

Data regarding field cancerization of prostate cancer is especially abundant. I can recall long ago, with the advent of PSA and during the early days of seed implantation, I would implant the classic prostate "B-1 Jewett nodule" which would regress (along with the PSA), only for another nodule to develop in the other lobe coinciding with a rise in the PSA.

We have since gained tremendous insight into the complexity of cancer mechanics as a result of the fast paced progress in histopathology, molecular biology and biotechnology as it relates to prostate field cancerization.
What we do know: at the time of diagnosis of an isolated prostate cancer, 90% of the remainder of the gland contains 2 or more cancerous foci (Human Path, Vol 41, No 6, 2010). So, while multi-focality most commonly pre-exists at the time of initial diagnosis of a single lesion, the entire prostate gland is subject to the same micro- and macro-environments which resulted in the initial cancerous lesion. Additionally, acquired genetic mutations further compound the rate of additional, future malignant tumor disposition within the gland over time ("metachronous disease"). Fascinating data suggests that the initial tumor itself even influences glandular tissue (via molecular alteration) to induce further oncogenesis within the prostatic glandular tissue, and even cancer progression at sites beyond the prostate. (J Mol diag, Vol 8, No 3, 2006).

Simply put, at the time of initial diagnosis, the <u>entire</u> prostate gland is at enormous risk for harboring additional malignancies ("synchronous disease").

The plethora of focal (and other) treatment options is likely a direct result of increased screening for prostate cancer. While the objective of wide-spread, annual screening is to find prostate cancer early enough to offer "cure," the challenge becomes delineating those men who actually *need* treatment from those who theoretically could survive without treatment. There has been righteous criticism of the fallout from screening – including too many unnecessary biopsies, too many unnecessary surgeries and radiation treatments, and the associated morbidities of these procedures, as well as the huge impact on healthcare costs. But is Focal Therapy the answer? Let's examine this in greater detail.

Focal therapies currently being offered for prostate cancer include:

**CRYOTHERAPY** Also known as "freezing," cryotherapy has been available long enough that there is now third generation technology in use. The original liquid-filled probes have been replaced with smaller probes filled with gas. The procedure involves regional or general anesthesia, and inserting probes via the perineum into the gland under ultrasound and thermosensor guidance. Activating the gas rapidly chills the tissue around the probe, causing cell destruction. Long term disease-free follow-up data is sketchy, but high incidences of impotence (as high as 87% in early studies) and incontinence have dogged the therapy. Increased rates of recurrence in the vicinity of the "warmed" urethra is all too common. Treating only a portion of the gland with focal therapy theoretically reduces the unwanted complications of total gland ablation, although no substantive long-term data exists.

**HIFU** (High Intensity Focal Ultrasound) Whereas cryotherapy uses freezing to treat prostate cancer tumors, HIFU uses thermal (heat) energy. Please note that HIFU is no different than hyperthermia which has been used for whole-gland treatment since the 1980's. Long ago, and including my own experience, it was determined that increased thermopathy was necessary (>90 $^{0}$ Celsius) in an attempt to improve local control. Despite this, recurrences were still extremely common, and complications were not uncommon (rectal/urethral fissures and fistulas, incontinence and erectile dysfunction). Using HIFU <u>focally</u> is new enough that few studies are available to report its success. Based on the high recurrence rates treating whole gland, results using focal HIFU would be predictable.

*As an aside, normal tissue obliteration which occurs with Cryosurgery and HIFU makes for extremely damaged tissues compromising future salvage treatment options (in contrast to radiation whereby normal tissues are repaired).*

**MRI LITT** (Laser Interstitial Thermal Therapy) Integrated with multi-parametric MR imaging, LITT is now being used as a treatment for focal, low-grade, organ confined prostate cancer. This modality is still in Phase I trials, that is, investigational, so no long-term data exists.
FLA (Focal Laser Ablation) This option, currently under investigation, uses laser energy to ablate lesions identified by MRI. A recent study involving <u>9</u> men found that MRI-guided biopsy post-FLA treatment found prostate malignancy to remain in 22%.

**BIPOLAR RFA** (Radiofrequency Ablation) Also under investigation, RFA can be performed under ultrasound guidance. A specially designed "driver mechanism" is used to position probes which emit radiofrequency waves to the target. As of 2015, no trials had reported RFA outcomes.

**PHOTODYNAMIC THERAPY (PDT)** uses a topical or systemically administered photosensitizer which accumulates in a target tissue, where it can be activated by light – which leads to generation of active radicals that attack cancer cells. A phase I trial using PDT in 15 patients with recurrent prostate cancer, using Foscan® as a photosensitizer saw PSA decrease in 9, but almost all eventually failed and required androgen deprivation therapy. Urethral damage and erectile dysfunction developed in approximately 30%.

**NANOKNIFE (IRE)** Irreversible Electroporation with/without Cryosurgery is a new, minimally invasive modality for the ablation of solid tumors. IRE takes advantage of the electric potential gradient that exists across cell membranes to create permanent pores in the cell membrane. The IRE generator sends electrical energy pulses that alter the cell's transmembrane potential, creating permanent nano-sized pores that irreversibly increase the permeability of the cell membrane, ultimately causing cell death. As with all new therapies, the value of this approach must be evaluated based on clinical research and publication of results. Combining this with cryosurgery will necessitate even further investigation.

**PROSTATE BRACHYTHERAPY** (seed implant) is, of course, the most practiced and studied "focal" therapy of all. Brachytherapy allows for intraprostatic tumors to receive much higher dose levels than other regions while nearby non-malignant regions can be sub-selected to receive microscopic dose levels or even a nil dose if planned. It is well documented that the DNA of normal irradiated cells undergoes complete repair, in contrast to the other aforementioned focal treatment options.

Proponents of focal therapies believe that their approaches offer the patient with low risk/low volume, low PSA, low Gleason score (≤6), an alternative to Active Surveillance and the accompanying stress and uncertainties it can put upon the man. ***I would make the argument that any man who is deemed a candidate for focal therapy should not be treated at all!***

These patients often make their treatment decision based on the standard 10-12 core ultrasound guided biopsies with or without fused multi-parametric MRI (mpMRI), although studies have determined that saturation biopsies are necessary for the most accurate staging.

In conclusion, focal therapy would be a waste of time, resources and effort for virtually every man. Moreover, these men will succumb to multiple future intra-prostatic recurrences, further biopsies, testing, etc. and the focal therapies' compounding side effects – which are the very things they hoped to avoid by choosing "focal treatment" in the first place!

October 2017