

MALE LUMPECTOMY: FOCAL THERAPY IS THE FUTURE OF PROSTATE CANCER TREATMENT

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INTRODUCTION

For both patients and doctors, current prostate cancer management reminds me of Oliver Hardy saying to Stan Laurel, “This is another fine mess you have gotten me into!” Relying on radical treatments with high morbidity, we seem to have abandoned the basic tenets of cancer therapy:

1. Find it early.
2. Stage it as accurately as possible.
3. Treat it aggressively, appropriate to its stage and tumor aggressiveness.

We find ourselves in a paradoxical situation. Early detection of prostate cancer has become difficult, if not impossible, due to new guidelines against routine PSA screening. Why did the U.S. Preventive Services Task Force, a volunteer panel of medical professionals, rule against wide use of a simple and effective screening tool? First, men with suspicious or rising test results are sent for an unpleasant diagnostic procedure (TRUS biopsy) that has been proven to miss up to 30% of cancers. Those with negative biopsies later have repeat biopsies, while expense (and anxiety) mount up. Second, this protocol finds too many less aggressive cancers—and the cure may be worse than the disease.

A dilemma between overtreatment vs. no treatment occurs when patients diagnosed with low-to-moderate risk cancer are counseled to defer treatment in favor of active surveillance, a strategy for which many patients don't have the psychological tolerance—they worry that a time bomb is ticking in their bodies. This worry may well be justified by a recent UCLA study showing how prostate cancer cells are a moving target. (1) Yet this advice is given so men can hold off on the risks of overtreatment: urinary and sexual side effects. So we don't go looking for cancer because we might find it, over treat it, and damage men's quality of life? Can you think of any other cancer for which early detection is discouraged and treatment delayed? It is extremely rare to suggest that other cancers (breast, liver, lung, kidney, liver, etc.) can simply be monitored!

My twofold thesis addresses this dilemma by offering a safe and effective middle ground:

A. For diagnosis, there is an alternative to TRUS biopsy that is extraordinarily accurate, painless, and does not involve puncturing the rectal wall. It is the 3D Transperineal Prostate Mapping Biopsy (3D-PMB), which is more disease-specific for low, moderate and high-risk cancers than MRI-guided targeted biopsies. It improves prostate cancer management decisions by up to 70% because it allows matching the treatment to the disease, and it provides specific localization for precise targeting. In short, it meets the first and second tenets of cancer therapy.

B. For treatment, there is an effective FDA-approved minimally invasive procedure that satisfies the third tenet of cancer therapy, to the major benefit of the patient.

THE MALE LUMPECTOMY

This article describes our latest results with both 3D-PMB and focal cryotherapy (cryoablation, or simply cryo, meaning lethal freeze). Our data validates the advantages of what I first termed the Male Lumpectomy.

I now have long term results (average follow up of 10 years) with focal cryotherapy for prostate cancer or the Male Lumpectomy. I first presented this idea in a 2002 paper (2) demonstrating that we could effectively locate and target a prostate tumor without having to destroy, remove or irradiate the whole gland. By isolating and treating just the tumor and a surrounding safety margin, we generate competitive (actually better) efficacy in controlling cancer while preserving healthy tissue to markedly lower morbidity (side effects).

That paper started the ball rolling. Focal prostate cancer therapy is now carried out in some manner in major U.S. cancer centers, including MD Anderson, Johns Hopkins, Sloan Kettering, Duke and NYU to name a few. Textbooks cover the subject and annual medical meetings on this topic are convened. The results are consistent: good cancer control, yet low side effect risks.

My own study data offers compelling evidence that mapping biopsy and focal cryo provide a combined clinical approach

that completely changes the current paradigm, meeting the highest cancer treatment standards, and bringing it fully in line with the best therapies for local treatment of any other tumor. Additionally, this approach greatly reduces the high economic costs of conventional prostate cancer treatments (robotic prostatectomy and radiation therapy), as well as the long term personal quality of life costs (with their own associated management dollars).

MATERIALS AND METHODS

In our practice, we stage patients for focal therapy using 3D Transperineal Prostate Mapping Biopsy (3D-PMB). Transrectal ultrasound (TRUS) guided biopsy is not enough to guide focal therapy. 3D-PMB is carried out under general anesthesia (so it's painless). Unlike a transrectal biopsy, which takes prostate samples through the rectal wall, 3D-PMB is done through the perineum (the skin between the scrotum and rectum). A grid, like that used in brachytherapy, is placed against the skin, and ultrasound guides the position of needles into the gland. Note that while ultrasound cannot distinguish important differences in normal and cancerous tissue, it clearly shows the placement of biopsy needles. Tissue samples taken throughout the gland are separately marked with the grid coordinates so their precise location is identified in the pathology report. This is what gives a three-dimensional or holographic map of any cancers, even very small ones that might be found. We are able to take far more samples than the 10-12 commonly taken in a TRUS biopsy. 3D-PMB also has the advantage of more accurate Gleason scores since there's little risk of missing a tumor core where the more dangerous cells tend to be.

A study we published in the most prestigious cancer journal in the world (*Journal of Clinical Oncology*) compared the results of TRUS biopsy vs. 3D-PMB in over 180 patients (3). What we found was sobering. Compared to TRUS biopsy, 3D-PMB found 50% more cancer on the opposite side of the gland. It also raised the Gleason score in approximately 25% of patients. Additionally, a 3D-PMB is safer than TRUS biopsy because it is a sterile procedure, greatly lowering the chance for life threatening sepsis (infection with colon bacteria) and debilitating prostatitis that are significant risks in TRUS biopsy. Identifying the exact location of each specimen allows *exact treatment targeting of the tumor, including its location, size and shape*.

Some clinicians are using MRI guided biopsies to guide focal therapy. Studies comparing MRI to mapping biopsy or prostatectomy specimens show that it misses 25% of significant cancers (4) and is only 28% specific, meaning that 72% of the time what it reads as cancer is not (5). While I support advanced multiparametric MRI of the prostate as an adjunct resource, only 3D-PMB can give the thorough tissue map necessary for long term cancer control as demonstrated by my data.

What about the concern that biopsies spread cancer? There is absolutely *no credible clinical evidence* that this happens. Why is this important? Fears of "track seeding" have been sadly overplayed by a handful of doctors who feed patients' wishful thinking that prostate cancer can be clinically diagnosed and staged by imaging alone. In fact, MRI or color Doppler is not specific enough to make an accurate diagnosis of prostate cancer, meaning it often OVER estimates less aggressive cancer, and is not sensitive enough in identifying very small but significant cancers. Anyone who tells you, based solely on imaging, that you have cancer is doing you a great disservice—especially if they proceed to treat you. It is my conviction that any physician who treats based on imaging and/or rising PSA without biopsy confirmation is committing the grossest kind of malpractice. In the last month I encountered two patients who had been offered radiation *without biopsy confirmation of cancer*. I was appalled, as this violates the universal medical ethic, "Above all do no harm" (*primum non nocere*).

In our practice, we originally theorized that perhaps 25-30% of prostate cancer cases would be amenable to focal therapy. Our experience, confirmed by another study (6), showed that as many as 94% of patients qualify for a focal approach. In other words, focal therapy is more than a "niche" treatment—many more men may benefit, especially when their disease is accurately diagnosed and staged, and when the treatment is done by an expert.

Once you have located the tumor there are a number of ways to kill the cancer. We mainly use cryotherapy (cryoablation or simply "cryo") to carry out the focal therapy. Cryo is the only ablation modality that has Level One evidence of superiority over beam radiation in eradicating cancer (compared in a randomized study) (7). Another excellent reason to use cryo comes from evidence of a specific tumor immunologic effect when a cancer is frozen. This effect has been shown in animal models to prevent metastatic disease and to cause regression of distant prostate cancer metastases (spread) in patients. Our cancer control results with medium and high risk patients are so much better than reported data with radical prostatectomy or radiation that an immunologic explanation for these results must be considered. Heat-based therapies such as laser and HIFU denature (destroy beyond recognition) tumor proteins (antigens). It is these antigens on the surface of cells that scatter into the body. Since they are not intact cells they cannot spread or cause cancer, but they are helpful because they appear to trigger this immunologic effect (8, 9). I predict it will take at least a decade to see if heat-based ablation gets the same immunologic results. Personally, I don't want to deprive my patients of this potential benefit, particularly when there is no advantage I can see, as yet, to other ways of killing the tumor.

FOCAL CRYO RESULTS

In our practice, we now have clinical data on a total of 70 patients who underwent focal cryo. All have at least 8 years follow-up (ranging from 8 to 18 years with a mean follow up of 10.1 years). 41 patients were Gleason 6 or less, 24 were Gleason 7 (6 patients 4+3, 18 patients 3+4) and 5 were Gleason 8 or greater. 15 patients had a PSA of 10 or greater. We stratified the 70 patients using the D'Amico system. Thus, 29 patients were low risk, 32 medium risk, and 9 high risk.

TABLE 1: PATIENT DEMOGRAPHICS		
Patients	70	
Follow-up	8-18 years	Mean 10.1 years
D'Amico Risk level		
Low	29	
Medium	32	
High	9	
Gleason score		
Gleason 6 or less	41	
Gleason 7	24	
Gleason 8 or greater	5	
Stage		
T1c	56	
T2a	6	
T2b	3	
T2c	4	
T4	1	
PSA level at DX		
less than 10	54	
10-20	13	
greater than 20	2	

Table 1. Risk stratification of patients treated with focal prostate cryoablation (N = 70)

Overall actuarial survival was 66/70 (94%), meaning 4 patients died from other causes. **Disease specific survival was 64/64(100%), meaning no patients died from prostate cancer.** This is a rather remarkable statistic given that the majority of patients in this series (41) were medium to high risk. It certainly illustrates that patients who are appropriate candidates for focal therapy are not taking a greater risk of death in choosing this avenue.

Overall Biochemical Disease Free Survival (BDFS, meaning no rise in PSA) was 89% (62/70). When broken down by risk level, BDFS for low risk patients was 90% (26/29), for medium risk patients 88% (28/32) and for high risk patients 89% (8/9). These again are rather remarkable results. For comparison, a 2012 article by Ginsburg, et al., looking at results of robotic radical prostatectomy with over 1100 patients had an overall BDSF of 72% at 5 years (10). **See Table 2.**

TABLE 2: RESULTS	
Overall actuarial survival N=70	66/70 (94%)
Disease specific survival N=70	70/70 (100%)
Biochemical Disease Free Survival	62/70 (89%)
BDFS High Risk (D'Amico)	8/9 (89%)
BDFS Med Risk (D'Amico)	28/32 (88%)
BDFS Low Risk (D'Amico)	26/29 (90%)
Bilateral Multi focal	19/20 (95%)
Local recurrence N=10	9/10 (90%)
Continent after primary procedure	70/70 (100%)
Retained potency	48/60 (80%)

Table 2. Survival and recurrence rates for focal prostate cryoablation (N = 70)

In my experience in a tertiary referral practice, having interviewed patients who have already seen surgeons, it is unusual to encounter a patient who has had explained to him what a “positive margin” is. For those who are unclear, after the gland is removed, the cut margins of the gland are stained and microscopically examined for tumor. If tumor is found at the cut margin the implication is that there is residual cancer left in the patient. This is called a positive margin. It leads to a high rate of disease progression. In Ginsburg’s study positive margins occurred in 27.3% of patients, which the authors describe as in keeping with national statistics. Our results, with selective tumor destruction while preserving healthy, functional prostate tissue, hold great promise for patients who might otherwise undergo surgery, with its risks of short and long term urinary and sexual side effects, only to experience a rising PSA within years of the treatment.

Why all risk levels of patients would have the same cancer control results, might have two possible explanations:

1. Focal cryo has an ability to treat extracapsular disease. Patients at high risk for positive margins at prostatectomy have a better chance of local control with ablative therapy. This was very well illustrated by one of our patients who had a T4 lesion already invading the bladder, a PSA of 200 and a Gleason score of 10. He is now 8 years out from his cryo with no evidence for recurrence. We also have used a localized removal of urethral tissue in some patients who had tumor next to the urethra, when we were afraid that the urethral warmer might prevent a completely destructive freeze at that site.
2. A cryoimmunological response must also be considered for these remarkable results in medium and high risk patients. Based on the human and animal data, it’s likely that in some patients there is exposure of tumor antigens at the time of the

procedure that acts as an in vivo cancer vaccine, preventing later metastasis from occurring.

A WORD ABOUT RECURRENCE

Choosing radiation or RP as a first or primary treatment limits future options. Neither has a good fallback position should local disease recur. Hormone ablation is not curative, and the side effects are unpleasant. However, when focal cryo patients are retreated they do extremely well. The ability to retreat patients with local recurrences by repeat freezing, or even RP or radiation, means that our patients have less chance of untreated local residual cancer that can later spread.

In our series, 10% of patients (7/70) were retreated with cryo to the **opposite** side of the original procedure. (In other words, a second cancer later occurred in previously biopsy-negative and therefore untreated tissue.) All 7 (100%) are biochemical disease free (BDF). Two patients with local recurrence underwent radiation and both are BDF. One patient underwent RP and radiation and is now on ADT (hormone ablation). In total, 14% of patients (10/70) had a local recurrence that required re-treatment, and 90% of those 10 patients (9/10) remain BDF.

Bilateral disease (cancer on both sides of the gland at initial treatment) was not a barrier to successful focal therapy. In our series, 28.5% (20/70) of patients had bilateral multifocal disease (more than one tumor location) that required bilateral cryo. Of those, 95% (19/20) were BDF.

FOCAL CRYO SIDE EFFECTS (MORBIDITY)

The hope for low morbidity associated with focal therapy has been confirmed by our results. **All patients were continent** (with **no** pads) immediately after the first procedure (100%). One recurrent patient converted to a second whole gland freeze, resulting in mild stress incontinence requiring pads while playing golf. Other authors confirm these continence results (11).

As to potency, focal therapy did extremely well. 58/70 patients were potent preoperatively (pretreatment baseline function). **54/58 (94%) were potent postoperatively with or without the use of oral agents, to their satisfaction**, within 6 months. However, 11 patients were ultimately rendered impotent by additional treatment (7 by additional cryo, 4 by a combination of ADT, radiation or radical prostatectomy). Interestingly, 4/12 preoperatively impotent patients were potent after the procedure. This was due to the immediate potency rehab protocol that we provide, if needed. 43/58 patients (74%) therefore ultimately retained potency. Again, these results are consistent with other focal therapy series. No other complications were noted. Blood loss was virtually zero. No rectal fistulas were seen and no patient needed a

further procedure for urinary obstruction.

CONCLUSIONS

The long term results of focal cryoablation, within the limitations of our data, is significantly superior to traditional RP and radiation. Unanticipated is that patients at high risk for recurrence have a much higher disease free survival than that reported with robotic RP and with better quality of life. Repeat treatment for localized recurrence does not appear to negatively impact patient disease specific or BDF survival, perhaps accounts for improved results in high and medium risk patients. Patients treated with bilateral multifocal disease appear to do as well as those with unilateral tumors. Most striking, all grades and PSA levels appear to have excellent results compared to other therapies. When including all risk levels of disease and bilateral disease, the overwhelming majority of patients would be eligible for this approach when appropriately diagnosed, staged, and treated by an experienced cryosurgeon.

The Male Lumpectomy achieves these results with minimal morbidity in terms of incontinence and potency. The safety and long term efficacy of focal cryoablation is now established, though this is not to say that further study is not needed. Enough evidence is available, however, that I would have no qualms about offering this option to qualified patients. Future investigators now have the data to have a comfort level to conduct comparative Level One evidence studies between focal therapy, robotic RP and the various forms of radiation.

This data also sets the bar high for focal therapy. When developing this approach, we tried to optimize every step of the procedure to give us the theoretically best outcomes possible with our current knowledge. All of the important aspects of our methods for selecting and performing focal therapy are supported by Level One data as being the best way to carry out this mission (3D-PMB for diagnosis and staging, cryo for the ablation). Since we are dealing with peoples' lives, anyone carrying out focal therapy should adhere to the principles we have outlined in selecting and performing the procedure. Based on my experience there will be a plethora of focal therapy methods being touted in the near future. It's going to take other investigators another ten years to figure out if their method can produce the same results. As a patient, you will be challenged to sort out proven treatments with a published, peer-reviewed track record vs. "the latest" innovations without long-term results.

We have been going down the same path with prostate cancer for so long. Despite the best efforts of urologic surgeons and radiation therapists to improve the results of their traditional treatments, little progress has been made in improving

survival and lowering complications. Focal therapy gives us a new, exciting and hope-filled alternative road to take. It will be the responsibility of the medical community to thoroughly compare focal therapy as we have outlined it, honestly and fairly, with traditional therapies. If this is accomplished I am confident that we will have embarked on a new era in prostate cancer management.

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