

Prostatepedia¹

¹expert insight + advice



Focal Therapy

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In this issue....

This issue is devoted to focal therapies. Interest in focal therapy is fueled by the promise of cancer control with fewer side effects than are seen after radiation or radical prostatectomy. From the patient perspective, this is certainly an attractive option. As a result, we have seen the development of an increasing list of approaches to focal therapy.

There are a number of issues that make critical evaluation of the various focal therapies problematic. First, with the exception of a recent trial that involved laser, randomized clinical trials are absent. There is even a controversy about what is the best control group. The laser trial just mentioned used an active surveillance control group. The second approach would be to randomize against surgery or radiation therapy. The major problem is that such trials have proved nearly impossible to run because of poor accrual. For this reason, I suspect that focal therapies are most likely to find a clinical niche as an alternative or add-on to active surveillance.

Another issue is that we lack trials that randomize between two different focal therapies, so it is difficult to know what approach to recommend for a given patient.

For example, cryosurgery and high-intensity focused ultrasound (HIFU) have both been around for many years and have never been directly compared in a clinical trial.

In developing focal therapies, it is currently common practice to treat a group of patients with a new technology and then follow those patients over time. Results are reported after 1, 5, and 10 year follow-ups and comparisons made to historical results with radiation or radical prostatectomy. However, we have long known that such comparisons with historical data are often unreliable. As mentioned above, a better, more time efficient approach would be to test focal therapies as an alternate or add-on to active surveillance rather than as an alternate to radical prostatectomy or radiation.

Charles E. Myers, Jr., MD

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Contributors:

- Editor-in-Chief*
Charles E. Myers, Jr., MD
- Publisher*
Jessica Myers-Schechter
- Copyeditor*
Lito Velazquez
- Proofreader*
Robert M. Protz, MS
- Transcriptionist*
Sarah Mason
- Designer*
Verity Burgess
- Community Outreach*
Corinne Halada
- Sales Consultant*
Rod Schechter
- Business Consultant*
Rose Sgarlat Myers, PT, PhD
- Editorial + Billing Offices*
274 Redwood Shores, #739
Redwood City, CA 94065
(800) 975 6238
- Administrative Offices*
PO Box 655, Earlysville, VA 22936

Scott Eggener, MD

Focal Therapy For Prostate Cancer



Scott Eggener, MD, an internationally known robotic and open surgeon, specializes in caring for patients with prostate, kidney, and testicular cancers.

He is the Director of the Prostate Cancer Program and Co-Director of the High Risk & Advanced Prostate Cancer Clinic at University of Chicago Medicine.

Prostatepedia spoke with him about focal therapy for prostate cancer.

Why did you become a doctor?

Dr. Scott Eggener: I came around to medicine later than most people. I always had an interest in science and math. The combination of being able to use those skills to help people out and to have a component of life that combines clinical care with research was ultimately the attraction that led me down this path.

Have you had any particular patients whose cases changed either how you see your own role as a doctor or how you view the art of medicine in general?

Dr. Eggener: I try to learn regularly from my patients. The overwhelming majority of cases are fairly routine

from a medical standpoint, but what makes my role fascinating are the unique elements of their background or hobbies and getting to know them. As far as memorable experiences, there are so many standouts from both the really heartwarming celebratory side and the profoundly depressing side. When you have a practice that focuses exclusively on cancer, you've got the highest of highs and the lowest of lows.



“The concept of focal therapy is to only treat the part of the prostate that has the cancer and leave the rest of the prostate alone.”



What is focal therapy? Where does it fit into the spectrum of treatments available to men with prostate cancer today?

Dr. Eggener: Focal therapy is a dense topic. The bird's-eye view is that, traditionally, any treatment of prostate cancer localized to the area of the prostate is focused on the entire

prostate. Unfortunately, the prostate is in ground zero of the pelvis where there are a lot of other important structures. Any treatment, even when done by a very experienced specialist, poses a risk of short and long-term side effects. The first and most important fork in the road is whether the cancer even requires treatment. Active surveillance, monitoring the cancer, is a very attractive approach for many men with an extremely low-likelihood of cancer-related problems.

The concept of focal therapy is to only treat the part of the prostate that has the cancer and leave the rest of the prostate alone with the utopian dream of limiting the risk of cancer-related problems while trying to optimize the quality of life and minimize exposure to side effects.

It's analogous to women with breast cancer. There was a time when every woman with any type of breast cancer had a radical mastectomy. Through good science, clinical trials, brave patients, and data nowadays, somewhere between 65 and 80 percent of women get a lumpectomy. We're in the very early stages of determining whether a similar strategy is safe and smart for some men with prostate cancer.

There are different forms of focal therapy: are some forms more effective than others?

Dr. Eggener: There are literally about a dozen different ways of ablating a part of the prostate. Focal therapy is a concept of treating part of the prostate. There are a lot of different mechanisms of trying to destroy parts of the prostate. There is not enough comparative data to say A is better than B or C is worse than D. There are some focal therapy interventions that have been studied relatively rigorously. Most have been studied in small populations of men. None have sufficient long-term follow-up, and none have ever been sufficiently compared to surgery or radiation therapy, which are the conventional and time-tested treatment options.



“There are a gazillion different reasons why focal therapy is controversial.”



Is that one of the controversies over focal therapy—that there's not enough long-term data to know which is better or not?

Dr. Eggener: There are a gazillion different reasons why focal therapy is controversial. Number one is that focal therapy turned the whole paradigm on its head in that prostate cancer is typically multifocal where about three-quarters of men with prostate cancer have multiple cancers within their prostate. Reflexively, a lot of people feel the entire prostate needs to be treated.

What we know based on elegant studies is the overwhelming majority of those other cancers within the prostate are not destined to cause any problems. There are many prostate cancers that are indolent, and if they are destined to cause problems, it'll be years or decades down the road. Some people are fundamentally opposed to the concept of treating part of the prostate. There isn't enough high-quality, long-term data to show whether the focal therapy paradigm is beneficial for certain men.

Conceptually, it's supposed to be helpful, but until we have proper clinical trials, that's just speculative. That is why there are dozens of clinical trials. Hopefully, one day we'll have quality data. There have been a lot of companies interested because it's attractive to patients. The FDA has recently gotten more engaged. There have been multiple public meetings with the FDA trying to figure out how best to evaluate focal therapy. There is a swell of interest, but it's going to take thoughtful investigators to provide the data. Unfortunately, as you know, in the landscape of prostate cancer there is often a lot of enthusiasm without data supporting it. Unfortunately, there are always charlatans willing and capable of putting the cart before the horse.

Is there anything about focal therapy that would prevent a man from getting a later treatment—i.e. a radical prostatectomy or radiation therapy?

Dr. Eggener: Conceptually, the plan is to do focal therapy and it doesn't necessarily burn any bridges. Theoretically, the more time that passes there is an increasing chance that in certain men the cancer can spread elsewhere in the body, although if you select men well



“We're still in the very early stages of properly evaluating this approach.”



for focal therapy you can minimize those risks. Depending on the type of focal therapy that's used, some have close to no impact on the efficacy of future treatments. There are other forms of focal therapy that are more aggressive and would impact the possibility of doing surgery or radiation in the future.

Do you have advice for men reading this who might be considering focal therapy?

Dr. Eggener: It's exciting conceptually but we're still in the very early stages of properly evaluating this approach. There are a range of practitioners who will offer focal therapy from very thoughtful prostate cancer experts with very selective criteria, clinical trials, and tempered enthusiasm to those on the other end of the spectrum—people who are one-trick ponies who believe nearly every man they see might be a candidate for focal therapy.

My advice to people is if you're newly diagnosed with prostate cancer and think focal therapy might be an attractive option for you, seek out someone who has expertise in prostate cancer who offers focal therapy amongst many other options and can thoroughly discuss the knowns and unknowns.

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Hashim U. Ahmed, MD

Today's Focal Therapy For Prostate

Dr. Ahmed is Professor and Chair of Urology at London's Imperial College Healthcare.

His research focuses on prostate diagnosis using novel imaging and tissue biomarkers, prostate treatments that reduce the harms of traditional surgery and radiotherapy, and clinical trials and health technology evaluation.

Prostatepedia spoke with him about the current state of focal therapy for prostate cancer.

Why did you become a doctor?

Dr. Ahmed: I decided to be a doctor when I was about 12 or 13. It was a simple matter of fact that I was just really interested in the sciences. I liked physics, chemistry, and biology. I actually enjoyed all of my subjects. It was the one area, the one profession where it seemed that you could branch out into a lot of things, once you got your degree. As well as the cliché: I want to help people. Everybody who wants to be a doctor wants to help people, but I think you can help people doing lots of things.

It was really the fact that it allowed me not necessarily to specialize too early and be able to carry on writing,

carry on looking at the different science topics, and get a greater understanding. It involves a lot of detective work. Subjects like geography and history are about detective work as well: looking at sources and verifying.

Have you had any patients whose cases have changed either how you see your own role as a doctor or how you view the art of medicine?

Dr. Ahmed: I think the key for me was, and this is a personal note, when I was going through medical school my father was diagnosed with colorectal and rectal cancer. He, both personally and culturally, really didn't like the impact of the surgery, and particularly the stigma of having a stoma. That stigma is still present to this day, but not as much as in those days, certainly. In fact, he ended up refusing to have the treatment. That was a powerful personal example of how patients can be put off from curative treatment because of the impact. They gave him a 5% chance of having a stoma, but that was high enough for him to actually refuse curative treatment.

I don't think at the time I saw it that way. It didn't really have that much of an impact on my thoughts as

a medical student or even in my early days as a doctor. Certainly later on, as I started to specialize and go into research because I had a natural curiosity to look at new things and innovate, that experience started to have an impact on what I was doing. My research over the last ten years, as well as my clinical practice, has certainly been about trying to meet the needs of patients. How can you make your practice and your research driven by not questions that you're interested in, which would be nice, but how you can improve things from the patient's perspective?

Sometimes the most cutting-edge treatment isn't something that the man himself finds of interest because of associated side effects?

Dr. Ahmed: Exactly.

What is focal therapy?

Dr. Ahmed: Focal therapy is about targeting the tumor within the prostate with a margin of normal tissue. The tumor is one that we believe that were we to leave it untreated, would progress, grow and spread, and impact the patient's life at some point. By doing so, we avoid treating the entire prostate. We avoid

damaging as much normal little tissue as possible. By damaging as little tissue as possible, we aim to maintain as much function as possible for that particular man, whilst at the same time treating the cancer that would otherwise cause problems in the future.

What are some of the various forms of focal therapy? Focal therapy is an umbrella term, is it not?

Dr. Ahmed: It is an umbrella term. I often joke that there's almost like a catwalk of treatments that can be used for focal therapy. The traditional ones were cryotherapy, which freezes the tissue, and high intensity focused ultrasound (HIFU), which uses very focused ultrasound waves that heat up the prostate. You can use laser, which also heats up the prostate. You can use electrocution of the cells, which is called irreversible electroporation. There are now some new injectable drugs. You can inject hormone drugs or molecules that are activated by PSA, which then kill the prostate cells once they are injected into the prostate. There's a lot of activity going on.

What I often say is that all of these different modalities are interesting. It's good to see that commercial bodies are really interested in this field. That shows that the concept has real legs and everybody sees this as a big future, so that everybody's crowding into the market. Ultimately, these are all tools, if you like—surgical instruments for me to do my focal therapy. No one tool can be applied to all tumors.

Let me take an example. If you had a big prostate with a tumor high up in the gland, there's no way HIFU would be able to reach it. The ultrasound wave just can't get that far. Even if it could, by the time



"I often joke that there's almost like a catwalk of treatments that can be used for focal therapy."



it reached the tumor, there would be so much tissue it went through that it would lose its energy. For that particular tumor, an anterior tumor, something like cryotherapy is probably going to be better for that particular man than HIFU. A posterior tumor near the rectum, but contained in the prostate, probably does really well from HIFU at the moment, but could easily be treated in the future using these injectable drugs, if they're to be efficacious.

Which form of focal therapy is best really does depend on where the tumor is, how big it is, and how big the man's prostate is. Are there other characteristics within the prostate, for instance, like calcification, which means you can't see the tumor? Those calcifications might, potentially, deflect the energy. There are a lot of other considerations, but there are quite a lot of things that you can use. I would say the two that are in pole position at the moment, just because they've been around for longer and therefore they have a lot of data, and the two that I use routinely in clinical practice, are HIFU and cryotherapy.

For which men is focal therapy usually an appropriate choice?

Dr. Ahmed: Firstly, focal therapy is a choice for the man who wishes to preserve or minimize his risk of genitourinary side effects like incontinence and erectile dysfunction

as much as possible. You could argue that everybody wants that, but there are some men who will just have radical treatment and say to me, "I understand that I have side effects, but I just want it sorted out." There are other men who prioritize minimizing the genitourinary impact that treatments have.

Focal therapy is also a good choice for men who have one index lesion. In other words, they have one tumor that is clinically significant, but at the same time have either no other tumors or one or two clinically insignificant cancers. In those men, we would target the main, biggest, or highest grade tumor because that is the one, studies have shown, that is likely to grow, progress, and metastasize if it was left on its own. The other, smaller, low-risk lesions are the type of indolent disease that a lot of men in the male population have that doesn't need immediate treatment. You can monitor those after you've knocked out the main tumor, for instance.

You wouldn't want to just knock out those one or two insignificant cancers while you were in there anyway because of potential side effects?

Dr. Ahmed: One of the reasons is it's difficult to localize one or two millimeters of low-risk disease. In order to treat those, you'd have to end up treating a block of tissue. By the time you'd treated that block of tissue, or two other blocks of tissue, you're probably at 70 to 80% of the prostate volume.

And if you do that, you might as well just target the whole thing?

Dr. Ahmed: You might as well just treat the whole thing because

you're going to cause as much damage. These small lesions are often not visible on MRI. They're found on random, systematic biopsies, and you have no idea exactly where they are.

Another consideration is the characteristics of the lesion itself that we would want to treat. It could be one of two things: intermediate Gleason Grade 7, so 3+4 or 4+3. Or, there's an increasing recognition that high volume Gleason Grade 6 is also something that is better treated immediately than monitored because that is also likely to progress. For unfavorable, if you like, low-risk disease and intermediate-risk disease where there is one index lesion you can carry out focal therapy. If you can have intermediate-risk disease, which has two or three significant lesions, you would be better served having radical therapy.

What happens if a man gets focal therapy and later his cancer recurs? Can he go on to other subsequent treatments?

Dr. Ahmed: This is quite an important topic now. We know that following focal cryotherapy, focal HIFU, and some of the newer emerging focal therapy modalities that about 15 to 20% of men will either have residual or recurrent disease in the area that's already been treated. Most of those men will be eligible to have a repeat session of HIFU or cryotherapy. Certainly in my practice, I tell men there is a one in five chance that we may have to repeat the focal therapy to the same area. Almost invariably, all men see that as just part of the intervention. I would argue having two treatments in a fifth of men is probably part of the treatment.

If they fail two treatments in that area, then they really should go on to have radical therapy, or a change in the type of treatment that you give. If the cancer has resisted 80 to 90 degrees centigrade temperature changes twice, or with cryotherapy minus 50/minus 60 degree centigrade twice, then that is an aggressive tumor. It probably has got a very aggressive blood supply and we need to change tacks.

There is a group of men who develop new lesions in untreated tissue. Some of those men can have another focal therapy, but most of them will go on to have radical therapy because their untreated tissue, if you like, has declared itself as unstable. It has a propensity to develop new tumors, and therefore, it would be better to treat the entire prostate.

About 15 to 20% of men over five to six years need a second focal therapy treatment. Overall, about 5 to 7% of men go on to have radical therapy, despite one or two focal therapy sessions. Now that is five to six-year data; we don't have ten-year data at the moment, either from HIFU or cryotherapy. The newer modalities don't even have five to six-year data.

Is it safe to say focal therapy is still an emerging option and that we still don't have all the data?

Dr. Ahmed: I guess it depends on how you define that level of evidence. If we have to wait ten to fifteen years, then yes. If you argue that we've now got good five to ten-year data showing non-inferior cancer control, superior toxicity, or superior side effect profiles after focal therapy, then there are a considerable group of men who will accept the uncertainty of the lack of ten to fifteen-year data.



“Which form of focal therapy is best really does depend on where the tumor is, how big it is, and how big the man's prostate is.”



They prioritize genitourinary function and they are not compromising their cancer control, at least at five to six-years median follow-up. And they can still have surgery or radiotherapy afterwards.

In the United Kingdom, in certain centers, focal therapy has been offered side by side with other radical therapies within the National Health Service, as part of the NICE, or National Institute for Clinical and Healthcare Excellence, approvals that we have.

What are some of the other controversies over focal therapy?

Dr. Ahmed: There are a number of controversies. One big controversy is this lack of ten to fifteen-year data. I was in the European Congress a couple of days ago. There was a Pro/Con focal therapy argument. I was pro and the person before me was con. He stood up and said, “We don't have fifteen to twenty-year data.” Five years ago, we didn't have five-year data. A couple of years ago, it was you don't have ten-year data. When we first started, they said well you don't have any one-year data on biopsies. This is the first time I've heard people stand up and say, well you don't have fifteen to twenty-year data.

It's slightly amusing. It's infuriating, as well, because the goalposts

keep on changing. The long-term data will come; we're collecting all the data in registries in the United States, the United Kingdom, and European centers. It's all very robust data collection. We're doing trials to see if men will accept randomization between radical and focal therapies. Those trials are tough. Men generally want to choose their therapy rather than allowing themselves to be randomized, but we'll see.

Then the other controversies are around the areas that we touched on. What happens to the untreated tissue? So far, about 4 to 5% of men over the five to six years of median follow-up that we have in our series of several hundred cases have developed new lesions in untreated tissue. Now, those are probably just tiny bits of Gleason 7 tumors that the biopsy and MRI missed that then subsequently progressed. Some of them will be new lesions, but some of them will be disease that was missed in the first place, which declare themselves later. By ten years, it might be higher. So far it's quite low.



“In the United Kingdom, in certain centers, focal therapy has been offered side by side with other radical therapies.”



One of the arguments against focal therapy is that this is a multi-focal disease. The untreated tissue is just going to show up with lots and lots of cancers, but that has not been the case, so that has been quite reassuring.

The other controversy is around the point that MRI is not good enough and biopsy is not good enough. But I think both MRI and targeted biopsy are good enough. You can never be 100% in anything. If you look at breast mammography, the data shows that a negative mammogram can miss anywhere between 5 to 30% of breast cancers, yet we still use it as a screening tool. We all accept that nothing in medicine is certain.

Then there's concern about what happens to men who fail focal therapy. Can we remove the prostate, or are these men too scarred. What happens in terms of their cancer control? It's early days yet, but certainly technically, removing a prostate after focal therapy is easier than removing a prostate after failed radiotherapy. It certainly is more scarred around the treated area, though. Does that mean men shouldn't have focal therapy? I would argue not because we're giving radiotherapy to hundreds of thousands of men. It's an accepted treatment modality, and if it does fail, it's tough surgery afterwards. That is, unfortunately, the nature of the beast. When the first treatment fails, secondary treatments are always going to be a little bit more difficult, if not a lot more difficult.

It is difficult to perform that second surgery or men will have more side effects after their surgery?

Dr. Ahmed: The concern is both. If it's more difficult to perform, then are they likely to suffer more side effects? And, as a result of the surgery being difficult, are we going to get more positive margins? Are they going to fail more often? These are men whose tumors are going to be very aggressive by nature because, as I said, they

resisted extremes of temperature, sometimes twice, and there are still a few cells. So they're going to be pretty aggressive. The failure rates might be higher in that group, just because of the focal therapy paradigm. Just like radiotherapy, when you get radio-resistant cancers they are generally more aggressive and nastier cancers just by natural selection, if you like.

Do you have any advice for men who are considering focal therapy?

Dr. Ahmed: It's very important when you are first diagnosed with prostate cancer not to rush into treatment. It's important to do as much reading as you can and have consultations with urologists and radiation oncologists. If you haven't been told about focal therapy, ask whether you're suitable. You might get an answer that says, “Well, it's not proven.” But if you are keen to explore it, you should definitely have a consultation with somebody who does focal therapy so that they can tell you first whether you are suitable, and secondly, what the outcomes might be in your case. I think every good focal therapist will share the uncertainties, as well as the certainties, around the treatment that they give.

If they're not sharing those uncertainties, then see somebody else. It's also very important that they quote their own data. That data, ideally, should be published in the public domain because that is a sign, first of all, that you're being told the right outcomes for that surgeon or physician. Also, it's a sign that physician takes their trade seriously and is constantly looking to see how they can improve, as well as sharing their data with their peers.

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Edward Schaeffer, MD

An Urologist's View Of Focal Therapy



Dr. Edward Schaeffer is the chair of the departments of Urology at Northwestern University Feinberg School of Medicine and Northwestern Memorial Hospital.

Prostatepedia spoke with him about focal therapy for prostate cancer.

Why did you become a doctor?

Dr. Schaeffer: I've always been fascinated with how things work. My fascination dates back to when I was a child who loved to understand the mechanisms that made an alarm clock work.

Over time, that interest in the mechanical nature of things evolved to an interest in the complexities of animals and living things. From there, I got intrigued by not just normal anatomy and physiology, but also by understanding how and why things break down. Restoring things to normal is one appealing part of medicine.

If you can understand why things fall apart, you can understand how to fix them. That is the essence of part of medicine. The other part of medicine is humanism, the ability to help people. It's truly such an honor to help people with their problems. I'm reminded of that privilege daily.

Have any particular patients over the years stood out in your mind? Any cases that may have changed how you view the art of medicine?

Dr. Schaeffer: I have an open style with my patients, and they can all reach me through my personal cellphone number. I give them my personal number because I view my position in their lives as a privileged one.

Patients come to me with a problem, and they really open up to me about their own health problems, their anxiety and fear, and the psychological impact that their new disease diagnosis has had on their life. Because they've been so open with me, I view it as part of my role as a physician to give them access to me if they need me.

I've developed personal and close relationships with all of my patients. I maintain objectivity, but the disease I take care of is a personal one. It's a cancer, and there can be a lot of emotional burdens that go with it. My patients are always changing my view of my role in medicine and my role in life and family. I've learned so much from them.

That's fairly unusual to provide your own cellphone number, isn't it?

Dr. Schaeffer: It's highly unusual! But I've never done anything based on what other people do. I just do what I think is right.

What is focal therapy, and where does it fit into the spectrum of treatments that are available to men with prostate cancer today?

Dr. Schaeffer: Focal therapy is one type of interventional treatment for men who have localized prostate cancer and for men who have localized prostate cancer that is contained within the particular focused area of the prostate. Generally speaking, when patients have a low-volume, low-grade prostate cancer, the first go-to option is typically a program of surveillance because we often deem these as cancers that don't require any active intervention.

But some patients want to do something or don't want to have treatment of their entire prostate, and so they may request that we focally ablate the suspicious or concerning area. That is a potential option.

When we do focal therapy, we always have to follow the patient

and monitor not only the area we treated but also the other areas of the prostate for cancers that may crop up.

In some ways, it's more intensive active surveillance because it's active surveillance plus something. On the spectrum, it's a minimalist approach, but the jury is still out as to whether it's an effective approach. While there are many anecdotes out there where people have thought it's been successful, it hasn't been widely studied.

Is that one of the controversies around focal therapy?

Dr. Schaeffer: Yes, I would say so. It has not been rigorously studied with one exception. One type of focal therapy, photodynamic therapy, has been studied in a prospective clinical trial. This trial was promising: it showed that focal therapy can reduce the amount of cancer and reduce the progression of cancer.

Are the side effects fewer with focal therapy than with whole-gland therapy?

Dr. Schaeffer: That is the idea of it. That is correct.

Let's say someone gets focal therapy and then their cancer recurs. Does the previous focal therapy impact or impede their ability to get another primary therapy like radical prostatectomy or radiation?

Dr. Schaeffer: It makes it more potentially challenging to do what we would then call definitive secondary or salvage treatment, but that's not true for every patient all the time.

When somebody has prostate cancer in one area of the prostate



"I have an open style with my patients."



and undergoes focal therapy, they're monitored for two things. One is recurrence or regrowth of the cancer locally. Second is the development of additional cancer in another area of the prostate.

Individuals who have had focal therapy may require additional treatment for one of two reasons. One reason may be that the area where the cancer was before was not effectively treated the first time. That would be disease persistence. Then the other reason may be that perhaps a cancer developed in another region of the prostate. We know that prostate cancer is a multi-focal disease, so it certainly is possible that a cancer could occur somewhere else. That is why people who have had focal therapy can't give up monitoring their cancer over time.

Any other controversies over the role of focal therapy?

Dr. Schaeffer: The main controversy in terms of focal therapy has to do with the fact that many consider focal therapy to be a treatment, that if you can detect the cancer on MRI, for example, you could focally treat the MR-visible area. There is good research from UCLA and other groups that shows that the volume of the cancer that was originally noted on MRI underestimates the true volume of the cancer by two or three times in some cases.

So, what should you treat? Should you treat only the MRI-visible area,


or should you treat the MRI-visible area plus a boundary of prostate around it because there's this possibility that cancer may extend beyond the MRI visibility? That's a big controversial area because the more broadly you expand your focal treatment area, the more you increase the possibility of having side effects from more extensive treatment.

Do you have any advice for men who are considering focal therapy?

Dr. Schaeffer: For all individuals with a new diagnosis of prostate cancer, they should really seek the advice of an expert. Somebody who's well-versed in all treatment options for prostate cancer would be very helpful.

I don't perform focal therapy myself, but I know experts who do. If I believe someone's a good candidate for it, or if I think that someone's not a good candidate for focal therapy, but they're still interested, I'll refer them to an expert so that my patients can get their advice. I think it's important that patients seek advice from an expert in the management of prostate cancer who can help them understand the full implications of the treatment options.

Would you encourage most patients to seek a second opinion?

Dr. Schaeffer: I do, unless their diagnosis was at an NCI-designated cancer center or hospital in similar standing. If they're at a center of excellence already, they don't have to go to a second one unless you're uncomfortable with your team. I think that the idea of seeking out somebody with expertise in that particular disease area is very important to get the best advice possible. 

Jonathan Silberstein, MD

Focal Therapy For Prostate Cancer

Dr. Jonathan Silberstein is the Chief of Urologic Oncology at the Tulane Cancer Center.

Prostatepedia spoke with him about focal therapy for prostate cancer.

Why did you become a doctor?

Dr. Jonathan Silberstein: I grew up in New York City. My dad was a pharmacist. He took every penny my family had and opened a pharmacy in the very late 1980s in Chelsea, which was a primarily gay neighborhood at the time. Since he took every cent that the family had, my job was to work at the pharmacy—nights, weekends, and after school. I spent many years doing that.

The pharmacy primarily ended up treating HIV-positive gay men. I worked there for many years. Then I took off a couple of years for college. I then started working there again during the summer full-time. These men, who I didn't recognize, were coming back and saying hello to me. I had delivered medications to their houses, or known them years ago, but all of a sudden I was now seeing men who looked transformed. They'd put on weight, they were going back to work, and they were living their

lives again. At that point in time, I saw the power of medicine to make a difference in people's lives, to change their lives, and I wanted to be a part of that. That's why I was interested in becoming a physician.



"I saw the power of medicine to make a difference in people's lives."



Have you had any patients over the years whose cases either changed how you see your own role or how you view the art of medicine as a whole?

Dr. Silberstein: Every patient. I'm lucky enough to still be dramatically influenced by every patient I have. From patients who have a deadly disease and we're able to make dramatic differences in their outcome and change their lives, to patients who have an indolent type of disease and we recommend dramatic changes in what their doctor was recommending before, to something as simple as putting a catheter in a patient with urinary

retention in the emergency room and taking someone out of tremendous pain: these can all be life-changing experiences for the patient and most of the time for the doctor as well.

So many times we miss Little League games and ballet recitals and often it's for something that feels very inconsequential, but every now and then you're able to make a big difference in someone's life and that can be a tremendous experience.

What is focal therapy? Are some forms of focal therapy more effective than others?

Dr. Silberstein: Focal therapy is the equivalent of the male lumpectomy. People are familiar with breast cancer: if a woman has breast cancer, often one of the management options is to remove a small portion of the breast as opposed to the entire breast. Since most men with prostate cancer have prostate cancer that consist of 1, 2 or 3% of their prostate, the idea of removing their entire prostate and the morbidity that ensues with such treatment, doesn't make a lot of sense intuitively.

If there were some treatment that we could offer where we treat just a portion or a fraction

of the prostate and we're able to eradicate the cancer and maintain 90-95% of the prostate without the detriment that we have through all of our treatments—loss of sexual function and incontinence—then we would be excited to proceed with those types of treatments. That is the idea of focal therapy.

In practice, focal therapy becomes much more challenging for a variety of reasons. First and foremost is that when we think about breast cancer, usually women have a spot on their breast that's large enough to be demonstrated on sometimes an X-ray but almost always an MRI. We can see the lesion. We can see the area of interest. And we can often even feel it when we do a good exam. With prostate cancer, it's much harder for us both to see it and feel it, and thus treating the appropriate portion of the prostate can be extremely challenging.

Also, the breast is on the external surface of the body, so the risk of hurting things near the breast, if we do a small surgery, are relatively small. The prostate is about as deep and central to a man as possible. The structures around the prostate not only influence erections and continence, but also influence our everyday functions like urinating or having bowel movements. Those are the obstacles.

Are the risks or the potential side effects of focal therapy as severe or less severe than with radical prostatectomy or radiation?

Dr. Silberstein: Just about every study that has evaluated focal therapy in any true scientific fashion has shown that the outcomes in terms of the risks of erectile





“In practice, focal therapy becomes much more challenging.”



dysfunction or urinary incontinence are dramatically reduced with focal therapy of the prostate.

If someone gets focal therapy and then their cancer recurs years later, can they then go on to radical prostatectomy or radiation therapy; or is there something about focal therapy that makes that second procedure more difficult?

Dr. Silberstein: Certainly, men who have had focal therapy can receive more radical treatment in the future if it becomes necessary. They can also receive more focal therapy, but the radical treatments are going to be dramatically more burdensome as a general rule to the patient. The chance of cure with those radical therapies appears to be lower for most of the published studies should that patient need to have radical treatment.

The idea of focal therapy is that an intervention can be performed on a part of the prostate with the intent of eradicating the disease, but on the off chance that the cancer comes back, radical treatment is still a possibility. That is true of most of the focal therapies that we’re going to discuss, but it’s imperative that we understand that those radical therapies become much more challenging and the outcomes become much more questionable.

While surgery is possible after focal therapy, surgery itself is much



harder, the risk of biochemical recurrence appears to be higher, and the risk of incontinence becomes much, much higher.

Focal therapy for prostate cancer is much less well characterized than focal therapy for breast cancer, radical treatments for prostate cancer, or even active surveillance for prostate cancer. We don’t know a ton about focal therapy as a scientific community. The reason we don’t know a lot about it is that most of the trials, most of the best scientific studies evaluating the outcomes of focal therapy, have been done on men who most of us believe don’t need any treatment at all.

Most of the studies have evaluated men who most of us would agree would be fine candidates for active surveillance. There have been very few studies that have looked at patients with higher-risk prostate cancer. We don’t really know the outcomes of those patients, because very few studies have evaluated them. Even for the low-risk patients, the studies that have evaluated the outcomes have done so in a less than ideal fashion. These studies have been largely retrospective. The few prospective trials have been single-armed as opposed to comparing actual outcomes. There is one randomized control trial I know of that looked at men who received a laser focal therapy of the prostate versus active surveillance. They were all men with low-risk prostate cancer. The risk of upgrading, of having worse prostate cancer on subsequent biopsy, appeared to be dramatically lower in the men who got the focal treatment. However, the study is relatively small and relatively early. (It was reported in *Lancet* in 2017 and likely will continue to produce very important results

in the future.) It’s tough to be overly enthusiastic about focal therapy as a modality of treatment without cautioning patients carefully about the limitations of the availability of data.

Focal therapy is a promise. We’re very excited about the concept of focal therapy. It intuitively makes a tremendous amount of sense, but we have very little data to support its efficacy. Many practitioners who offer focal therapy have little data to support what they’re doing.



“Most of the studies have evaluated men who most of us would agree would be fine candidates for active surveillance.”



Given that, would you suggest to men that perhaps focal therapy is still best considered as part of a clinical trial?


Dr. Silberstein: I would, absolutely. I would say that a lot of doctors out there are performing various focal treatments for prostate cancer. Focal therapy is best when combined with an academic trial that involves an imaging modality of the prostate. The ideal imaging modality is probably an MRI of the prostate combined with repeat biopsies in the future, regardless of what’s going on with the PSA or how the patient is feeling. That will give us much more confidence to move forward.

I would also say that very few doctors who are doing focal therapy are really doing it within that context.

That means that we’re never going to have a lot of good data helping us understand who is a good candidate for focal therapy, how we should move forward with this treatment, what is the right time to re-biopsy these patients, what are clear indications that the cancer is beginning to progress, or what is the right treatment after these men have progressed. We’ll never get that data unless we carefully study this moving forward as a community.

Do you have any final thoughts or advice for men considering focal therapy?

Dr. Silberstein: There are a smattering of clinical trials out there. The power of academic medicine is that we can do things that others may not be able to do. I would encourage people who are seeking focal therapy for prostate cancer to consider going to an academic center and enrolling in a clinical trial. I would certainly encourage them to make sure that they get imaging along with their focal treatment, and that that focal treatment should be directed at a specific lesion seen on some sort of image as opposed to just blindly stabbing at the prostate.

If people are curious about what treatment to use—i.e. does it matter if I freeze the prostate, heat the prostate, or use a laser to ablate the prostate—the answer is that until we gain a better understanding of focal therapy, I am personally agnostic in terms of what energy we deliver to the prostate to destroy the cancer. I think we’ve clearly demonstrated that we can safely eliminate the cancer with a bunch of different energy modalities, but I think the key to it is doing it safely under direct vision. 



Clinical Trial: Focal Therapy Outcomes

Dr. Jim Hu is a urologic oncologist at Weill Cornell Medical College, where he serves as the Director of the LeFrak Center for Robotic Surgery and the Ronald P. Lynch Chair in Urologic Oncology.

Prostatepedia spoke with him about a focal therapy clinical trial that he's running.

What was it about medicine that drew you in?

Dr. Hu: I was born in Taiwan and immigrated to the United States at the age of five. My mother got a Nursing Visa to come here during the nursing shortage in the 1970s. Immigrants tend to gravitate to something that's science-oriented like medicine. There was always a lot of cultural respect for medicine, and a healthy push from my parents led me to pursue it as a career.

Have you had any patients over the years whose cases have either changed how you view your own role as a doctor or how you view the art of medicine as a whole?

Dr. Hu: As a surgeon, sometimes we treat patients who develop unforeseeable complications that aren't directly related to the procedure. I remember operating

on a man who had stents put into his coronary vessels 6 months prior. This was 10-years ago, before more was known about whether to stop blood thinners. He received clearance from his cardiologist to stop his blood thinner, and then he suffered a heart attack during the surgery. Those types of unexpected events certainly stick with me. Surgeons gain judgement through experience, sometimes the not-so positive ones, and the most important decision is when not to intervene.

What is the context for your clinical trial?

Dr. Hu: If you look at breast cancer surgery about 40 years ago, for instance, some of the trials were done to demonstrate that a lumpectomy or a partial mastectomy in many cases was as good as removing the breast entirely. In prostate cancer, focal therapy or partial gland ablation is referred to often as the *male lumpectomy*.

The challenge for why there hasn't been a partial gland approach with prostate cancer is the timeline of knowing differences in outcomes. If you took a whole gland versus a partial gland approach, you're not going to see it as quickly as you might



in breast cancer, where metastasis or death can occur in a shorter time. In prostate cancer, 95 percent of men who are diagnosed are still alive 10 years after their diagnosis.

In about 75 percent of men who are diagnosed, prostate cancer is multifocal, so even if on a biopsy you find it in one area, it's not uncommon that when prostate is removed surgically, the pathologist detects prostate cancer in multiple areas. That's also been a barrier to the use of partial gland treatments in prostate cancer, and multifocality is less common in breast cancer.

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“Focal therapy or partial gland ablation is referred to often as the male lumpectomy.”

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When you're treated for prostate cancer, the blood test biomarker to determine whether you're free of cancer is the prostate-specific androgen (PSA). In contrast to other cancers, when you're treated for localized disease for instance, you don't do CAT scans or X-rays

to see if something has grown back or spread because the PSA is going to become detectable before there's any radiographic signs of a recurrence. Therefore, if you only treat part of the prostate, the part that's untreated, the normal prostate is going to continue to produce PSA. Therefore, the PSA is not going to be a meaningful marker of cancer recurrence with partial gland ablation. There are many unknowns in terms of how we should follow these patients who have partial gland ablation approaches.

What has driven the greater interest or the increased realization of partial gland ablations? MRIs are done commonly in the United States when men have an elevated PSA as a biomarker or as a predictive test beyond an elevated PSA of what the biopsy may show. This may help them forego a biopsy, but MRI's increased sensitivity or accuracy for finding significant cancers is about 70-80%.

Fusion-guided platforms take the MRI and fuse them to the ultrasound, which allows us to better pinpoint where the suspicious area is within the prostate. These fusion-guided platforms have enabled a more accurate diagnosis within the prostate. This has led to the application of these MRI ultrasound fusion platforms to deliver energy to kill cancer cells that have been confirmed in those areas. In other countries around the world, there has been availability of one of the partial gland approaches, high-intensity focused ultrasound (HIFU).

Before 2015, when the FDA approved HIFU for treating prostate cancer in this country, it was pretty common for men who were seeking partial gland treatments to fly overseas and pay out-of-pocket for these treatments.

We know that HIFU kills prostate tissue, but we don't know what the outcomes are for prostate cancer, and therefore, the FDA has not given a prostate cancer indication. You can't market it as treating prostate cancer, and because of the absence of comparative data to other treatments, Centers for Medicare & Medicaid Services (CMS) will not reimburse the full amount for prostate cancer treatment currently. Other insurances follow the lead of CMS. It's an interesting time. There is a need for comparative effectiveness research for clinical trials that compare this new treatment option of partial gland ablation to established methods of surgery, radiation, or active surveillance.

What can patients expect to happen in the trial?

Dr. Hu: In our trial, you have an MRI and a biopsy within 6 to 12 months after you get partial prostate gland ablation. There may be a tendency for people to get treated and never come back, assuming that the treatment was successful. This would almost be like receiving a placebo and not wanting to receive bad news if cancer returns.

Typically, a clinical trial means that we're offering a treatment to a patient. We don't really know the long-term outcomes. Therefore, there is a defined follow-up. Participants agree to get treated so that we can study this and clear up some of the uncertainty for others in the future, and so that we can detect a cancer recurrence earlier with structured follow-up. Data and outcomes are tracked as they occur, or prospectively to ensure complete collection of outcomes. We want a control group in which the patients

get standard treatment and we want an experimental or an intervention group who receives the new or novel treatment. This balances differences in characteristics such as age, race, other medical issues such as diabetes, cancer characteristics, etc.

The challenge with trials in prostate cancer is that few men would agree to having their fate based on randomization. If we said to your average American man with prostate cancer that we'll flip a coin, and if it's heads, you'll receive partial gland ablation, and if it's tails, you'll get surgery, they wouldn't go for it. This is reinforced by 11 randomized trials in localized prostate cancer that have failed to recruit. In this case, it's also a bit of comparing apples to oranges in the sense you're comparing treating part versus treating the entire prostate. Therefore, the side effect profiles are different in terms of incontinence, erectile dysfunction, and so forth. It's a space that needs more studies because there are many men who are interested in this technique.

One of the unfortunate aspects with men travelling overseas for HIFU is that we don't know what they're getting. We know of instances in the United States where practitioners are marketing a laser approach to prostate cancer, and men are paying \$25,000 out-of-pocket, but there are too many unknowns. Another example is laser treatments of prostate cancer which are advertised online or on billboards. These need to be studied thoroughly.

Unfortunately, the out-of-pocket nature of non-coverage by insurance distorts incentives with out-of-pocket payments for new technologies that are unproven and may not be studied thoroughly in that fee-for-service environment.





“In our trial, you have an MRI and a biopsy within 6 to 12 months after you get partial prostate gland ablation.”



If men want to participate, what would be the next steps?

Dr. Hu: If men want to participate, they may receive partial gland ablation if their cancer characteristics are not too severe. We may use cryotherapy, which is FDA-approved for a whole gland treatment of the prostate, and in many instances, insurance covers this. Or we may use HIFU, which patients often have to pay for out-of-pocket because insurances don't cover that. There is no randomization because patients have self-selected themselves to treat this. We are also involved with laser therapies as part of a study funded by the National Cancer Institute that is led by Dr. Leonard Marks at UCLA.

We counsel them about the side effects. Within a five-year period, up to 30 percent of them will need some sort of treatment, which we know because we find on subsequent biopsy that there is untreated cancer in other parts of the prostate or next to the areas that we treated. We're very transparent about that.

We're also transparent about the side effects that they may experience. Older men who have good sexual function going into surgery may find that their sexual function is a little diminished. That's not the case in younger men. Moreover, we haven't found that anyone



is incontinent after partial gland ablation, so that's a benefit.

We are working with the Food and Drug Administration (FDA) because they are confronted with a lot of new technologies and device manufacturers that want to do clinical trials and therefore have data to support the use of their technology with a prostate cancer indication. It's not unforeseeable that some of these new technologies to ablate the prostate tissue for other indications would be applied to prostate cancer. We're also working with collaborators at Johns Hopkins to establish a registry with data elements that the FDA wants for these new partial gland ablation technologies.

Our goal is to work with the FDA, industry, patients, and patient advocates to capture standardized outcomes so that these new technologies can be studied. It suits the needs of patients because it informs them of the outcomes. It suits the needs of device manufacturers who want to work with experts in both the community and academia, who are partnering with the FDA to clearly define when biopsies should be performed, for instance, and when there should be an MRI that could capture side effects and adverse events. It also suits the need for payers to define comparative outcomes so they may evaluate the effectiveness of partial gland approaches to inform coverage decisions.

How many patients are you looking to enroll?

Dr. Hu: We don't have a set number. Because of cost constraints, when the industry performs a clinical trial, they work with the federal government, for instance, to figure out if the study is appropriately powered to

For more information...

Contact Dr. Jim Hu
at jch9011@med.cornell

look at your end points. We're not at the point where we're designing any randomized control trials or participating in one yet, and so therefore I can't say that we have a sample size in mind.

It's an observational registry until there's a randomized trial, which I don't foresee happening for some time because of the challenge in achieving both physician and patient equipoise, which means an open-mindedness to one approach or the other.

We are trying to capture things that are already being done out there, patients who are already self-selecting treatment, so that we can learn more about what the outcomes are in terms of cancer control, adverse events, and quality of life.

If a man reading this is interested, should he contact you?

Dr. Hu: Absolutely. One should seek treatment with providers who are genuinely interested in cataloguing and characterizing how well the treatment works and how the treatment may not work. Ideally, those who are willing to put their outcomes into a coordinating registry network in a transparent manner that will help inform other patients, doctors, the FDA, industry, and payers about the outcomes of this new treatment for prostate cancer. ^{pp}



Patients Speak

Nick Massetti:

My Focal Therapy Story



Nick Massetti talks to Prostatepedia about his experiences with cryotherapy.

How did you find out you had prostate cancer? What was your reaction when you learned of the diagnosis?

Mr. Nick Massetti: I'm an engineer, and so the first thing I did was educate myself and look into whether I had a level of prostate cancer that needed attention. I learned about what PSA means, what the Gleason score is, and I read a couple of books.

The most important thing was going to a prostate cancer support group and hearing from people who had gone through the experience.

Some of them had pretty negative experiences. That told me to be careful about what I was doing and the kinds of advice I would get from the professionals.

Did you find the support group before you chose an initial treatment?

Nick: Yes. I joined the support group after I learned that I had cancer, before I chose the treatment.

From the group, I got references, I learned the names of doctors in my region who were more proficient and knew more about prostate cancer, and I learned to be a bit leery of urologists. They basically said urologists didn't handle prostate cancer that much.

That's interesting. Many men find a support group after they have been through treatment, but you went to one before and used the collective wisdom of the men there to help you zero in on a treatment and a specific doctor?

Nick: Yes. I wouldn't have known that there is such a wide variety of treatment choices if I hadn't gone there. Cryotherapy, which is what I ended up choosing, wasn't on my radar. It wasn't mentioned by any of the professionals that I had gone to see.

How did you find the support group?

Nick: The local chapter of the American Cancer Society held a monthly meeting, and I would go to it.

How did you choose that specific form of focal therapy? Why was it attractive to you?

Nick: Focal Cryotherapy was attractive because it wasn't surgery or radiation. The guys in the group had had some pretty bad experiences with surgery and especially with the after-effects of radiation that didn't show up immediately but six months later.

First, I looked into high-intensity focused ultrasound (HIFU). I was actually leaning that way, even though I would have had to go out of the country and spend \$25,000 plus travel costs. I followed that path for a while before I came across cryotherapy.

I had gone to Dr. Shinohara at UCSF. He had color doppler ultrasound, and he used it to locate the tumor and get a precise biopsy. The pathology report said Gleason 7, a level that needed action. When I went back to him for his advice, I asked him if he knew about cryotherapy, which he had. He'd done about 20 treatments in the previous 10 years. He said my case was amenable to that particular procedure, but he hadn't advised me towards it because he thought it was a little more experimental than this traditional stuff. That was fine.

When I went back to the prostate cancer group, they mentioned Dr. Duke Bahn. They knew of his work. I chose to consult with Dr. Bahn because I learned he had done 2,000 rather than 20 treatments!

I went down, saw him, and he imaged the tumor with his improved color doppler ultrasound system. Dr. Bahn said he respected Dr. Shinohara, so he didn't redo the biopsy, but he suggested what he

had in mind would work, and he felt as though he could take care of the tumor, which was localized just in half of my prostate, while leaving the other half alone. That was pretty much it. I had it done pretty soon after having that interview.

What was the procedure like?

Nick: I showed up the day before the procedure to do intake and then went to a hotel. The next morning, I returned at about 5:00am. They prepared me and I was put under anesthesia. An hour later, I was up and back in a hospital room. It only took an hour.

For the procedure, the doctor has a special catheter that prevents the urethra from being frozen and keeps it warm. He has a needle with an argon jet on it that's high pressure and when it expands it freezes nearby tissue. He takes that needle and freezes the area that he's interested in. He freezes it, let's it thaw out, and then he freezes it a second time. Apparently, freezing it twice kills the tissue, so the tissue is dead, but it stays there; it's not removed or anything.

I was up that afternoon walking around. The following day I took myself back to Los Angeles airport and flew to San Jose. I was back at work the next day. Monday, I showed up. Tuesday, I got the procedure. Wednesday, I flew home. And Thursday, I was at work.

Was there any discomfort or pain?

Nick: The only discomfort was having to carry around a bag that the catheter was attached to. That was a little bit uncomfortable, especially on the airplane. That Saturday, I went down to my

local ER and had them pull out the catheter, and I was pretty much fine. I had a little bit of bleeding over the next week but that was about it.

It doesn't sound bad at all.

Nick: Yes. I went back to Dr. Bahn after six months, after a year, and then after two years. He would do his color doppler ultrasound to image what was going on in there, and he said it was textbook. The region that he had treated showed no activity, and the other half was fine, so everything was very good.

You said the cancer's gone, and you're monitoring it every six months? How do you feel about how things are progressing?

Nick: I make sure that my doctor does a PSA test along with my standard cholesterol test every six months. I watch those. They're typically 0.8 nanograms per milliliter. That's about the right level for half a prostate, and it hasn't changed since 2012.

I'm pretty confident that whatever I had is gone and not coming back. And I'm also pretty confident that the PSA will be enough to let me know if it has returned, so I don't think about it much anymore, except to help other people. I'm still connected to folks in the support group.

I've had many people call and ask about my treatment because they're trying to decide what treatment they want to get. I just recommend that they consider it, look at the data, and decide for themselves.

Now you're counselling other men?

Nick: Yes, definitely.

Is this a formal part of your support group, or do people in your community know that if someone has prostate cancer and needs to talk about it, you're open to talking about it?

Nick: I let anybody know that they can refer me. I think Dr. Bahn's office actually referred a patient to me to talk about it because I told them they could give out my information. I have absolutely no problem talking to people about it.

What kind of advice would you give to a man who's in a similar situation to the one that you were in?

Nick: I'd tell them to keep measuring their PSA. I'd also ask them about the PSA because that's the cause of their concern. From all the research that I've done, if they don't have a PSA that's climbing, then it may not be something that they need to look too seriously at. Most of the doctors will see a high PSA and tell them to go get a biopsy, and that may or may not be what they ought to do because getting a biopsy can have dangerous side effects.

Then I counsel them to find the best doctor, and I recommend the ones that I used on the West coast, but I know there are many others.

I tell them to find a group like I did, so they can get the local information about doctors and also talk to people who have gone through the various types of treatment. They'll learn more questions to ask the doctors when they go talk to a doctor about the treatments. I give them the titles of the books that I bought and read, and I tell them to go buy those and read them quickly. Basically: get informed.

Do you still keep abreast of the prostate cancer news that's coming out?

Nick: I've attended the big Prostate Cancer Research Institute (PCRI) patient conference although usually just for just one day. That will catch you up pretty quickly.


I also look at the news, but I don't do much more than that at this point. We have a local prostate cancer support system in Irvine, Orange County, there's a hospital there that has a prostate cancer monthly meeting. I'm on their list, so I see what subjects they're talking about. I go to that once in a while.

I would call that staying informed! Some people don't even do that. I think there's a tendency for men to get their initial treatment and then just forget about it. But there is something to be said for keeping abreast of what's happening so that, if your cancer does come back, you know what to do.

Nick: I have six male first cousins who are my age and two brothers, and my uncles had prostate cancer. They lived into their 90s, and they didn't die of prostate cancer, though they certainly had it when they died. So it runs in the family.

I made sure all those other guys knew what to do. I sent them a letter about my experiences.

What was their reaction to your letter?

Nick: Basically, they said: "Thanks." I don't know... I guess people just don't think it's going to happen to them, but when it does, they know to call me. 



Merel Nissenberg: Focal Therapy Of Prostate

Traditionally, prostate cancer has been treated with either radical prostatectomy or whole-gland radiation. However, with the growing sophistication of MRI's and other imaging modalities, we are now able to identify cancer that exists in only a small portion of the prostate. There are now different types of technologies that have been developed to treat just the tumor itself; these are called focal therapies. The best scenario for focal treatment of prostate cancer is one in which the prostate cancer has an identifiable, single focus within (and not involving) the entire gland, and when the tumor can be accurately localized. As long as the cancer can be identified and treated without treating the entire prostate, and when the patient can be monitored for a long time, focal therapy can be an ideal modality for dealing with the disease. The rationale is to destroy the cancer while leaving healthy prostate cancer tissue surrounding the tumor.

Focal treatment is best for intermediate-risk prostate cancer (Gleason 7) that is found in only a single area of the prostate. This equates to about 30% of

newly diagnosed prostate cancer cases. There are several different types of focal therapies currently being utilized: Cryotherapy; HIFU (high-intensity focused ultrasound); Focal Laser Ablation; Photodynamic Therapy; and Irreversible Electroporation. However, it should be noted that these are relatively new therapies, meaning that long-term data with oncologic results is still needed. Some of the different modalities are described below.

Cryotherapy

Cryotherapy was the first type of focal therapy employed in prostate cancer, beginning in the mid-1990s. It involves placing cryoprobes into the prostate with the patient under general anesthesia and then creating an iceball that surrounds the tumor. Cells within the prostate either die immediately from the cold temperature or later from an inflammatory response. However, it is difficult to monitor the ice ball in real time, and measurement and control are difficult.

HIFU

HIFU was first used in prostate cancer in 1995 and is FDA-approved just like cryotherapy to treat prostate tissue. Targeted prostate cancer cells absorb ultrasonic waves and convert them to heat



which kills or damages the cells. Unfortunately, prostate imaging in real time remains an issue. While HIFU was first used to treat the entire prostate gland, it is now used as a form of focal therapy. Cancer-free rates upon re-biopsy have been very encouraging.

Focal Laser Ablation

Focal Laser Ablation involves placing a needle-like probe into the tumor with imaging as a guide. The laser heats the tissue to a high enough temperature to cause cell death. In two recent small clinical trials at UCLA, out of 10 patients only 3 had no residual cancer at biopsy; however, a third clinical trial is in the works there that utilizes a focal laser ablation device better suited to measure tissue destruction. While general anesthesia used to be required, patients now can have focal laser ablation with only local anesthesia.

Photodynamic therapy

Photodynamic therapy is another form of focal therapy, involving photosensitizers given intravenously that are activated by light. Free radicals thereby created go on to damage local blood vessels and tissue. This is an exciting method of tissue destruction but there is little data so far to demonstrate its

efficacy in prostate cancer. However, in a small study of 85 patients, 74% were cancer-free on biopsy 6 months later.

Electroporation (irreversible)

Electroporation (irreversible) uses electric currents between multiple small probes within the prostate in order to destroy prostate tissue by creating holes in the cell walls, which causes cell death. There are no large changes in temperature of the treated tissue, unlike the other methods of focal therapies.

At the March 2019 European Association of Urology meeting, Dr. Laurence Klotz from Toronto presented early findings from the 115 patients enrolled in the TACT Study, looking at MRI-guided Transurethral Ultrasound Ablation (TULSA) for patients with localized prostate cancer. TULSA is a minimally-invasive and MRI-controlled technology. 95% of the enrolled patients met the primary efficacy criteria of equal to or greater than a 75% reduction in PSA. Median drop in PSA was 95% from baseline. More studies have begun with this modality.

In conclusion, in low-volume, intermediate prostate cancer, focal therapies remain a potential type of treatment in appropriate patients. However, much more data is needed, as well as long-term follow-up, in order to be confident about the results. [PP](#)



274 Redwood Shores, #739
Redwood City, CA 94065
(800) 975 6238
info@prostatepedia.net
www.prostatepedia.net

Coming Up!

*May:
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