

Prostatepedia¹

¹expert insight + advice



Focal Therapy

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In this issue....

Last month we reviewed the impact of new tools like imaging on treatment choices for newly diagnosed men. We discussed how improved imaging impacts planning of both radiation therapy and surgery, as well as the role imaging plays in active surveillance in terms of patient selection and monitoring.

This issue is a logical extension of those conversations as we look at focal therapy treatment options based on those imaging tools. The renaissance of focal therapy is due to MRI, which has the ability to visualize cancer within the prostate gland with much greater precision than older techniques.

Focal treatment makes sense when the cancer is of limited extent, usually limited to a single major lesion on one side of the prostate. If the cancer is truly limited to only part of the gland, it may not be necessary to destroy the whole prostate. The hope is that focal therapy will have less impact on sexual function and urination than radical prostatectomy or radiation therapy to the whole gland. A frequently used analogy is a lumpectomy versus mastectomy for breast cancer.

As you read the interviews, there are a number of issues to keep in mind. With radical prostatectomy and radiation therapy, we know in detail

the odds of long-term cancer control. This information is lacking for the various forms of focal therapy.

One reason that cancer control might be less complete after focal therapy is that focal therapies largely depend on the ability of the MRI to identify patients with cancer limited to one area of the prostate gland. But, as we learned last month, the MRI is not a perfect tool and can miss small, aggressive cancers. Also, first-rate MRI facilities with well-trained radiologists are limited in number.

As a medical oncologist, I have recently had to deal with a particularly difficult situation. With the arrival of new, highly sensitive imaging for metastatic disease, such as the C-11 Acetate, fluciclovine F 18, and PSMA PET/CT scans, I am seeing a growing number of patients who have had radiation therapy and the only detectable recurrent cancer is in the prostate gland. Focal therapy in this setting is difficult because of radiation damage to surrounding normal tissue as well as dense scar formation within the gland. Several interviews touch on treatment options for this situation, but those options are far from ideal. It is unclear what the right path is for these men.

Charles E. Myers, Jr., MD



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Guest Commentary

E. David Crawford, MD



E. David Crawford is the distinguished Professor of Surgery, Urology, and Radiation Oncology, and Head of the Section of Urologic Oncology, at the University of Colorado Anschutz Medical Campus as well as the driving force behind <http://www.pcmarkers.com/>.

Dr. Crawford frames this month's discussions on focal therapy for prostate cancer.

There is a lot of interest in focal therapy right now. Years ago, when I used to recommend radical prostatectomy and radiation to patients, they would ask why I couldn't just take out a part

“Focal therapy hinges on our ability to effectively biopsy patients.”

of their prostate and not the whole thing. I would chuckle and say, “You can't do that.” I'd say that prostate cancers tend to be multifocal. We can't just operate on *part* of your prostate. We have to treat the whole thing.

That resonated with many urologists for years. Then Drs. Gary Onik and

Winston Barzell started using cryotherapy to ablate prostate tumors and mapping biopsies to localize the cancer. Like a lot of things in medicine, there was a backlash of people who felt focal therapy was inappropriate because prostate cancer is multifocal.

Dr. Onik persisted. When somebody came in with a low-grade or even intermediate-grade prostate cancer on the left side of the prostate gland, he would biopsy the right side of the prostate extensively. If there wasn't any cancer, he would do an ablation and treat the whole left side. That was the beginning of focal therapy.

I became interested in what I call *targeted focal therapy* about 15 years ago. Of course, focal therapy hinges on our ability to effectively biopsy patients so that you know you're not missing other, more aggressive tumors. Focal therapy means focally treating a lesion, but I like the term *targeted focal therapy* because we're targeting exactly where the tumor is with our mapping biopsies.

There are many ways to do focal therapy. We can use lasers, cryotherapy, or high-intensity focused ultrasound (HIFU). We're working on using immunotherapy to target lesions. We can even put alcohol into the lesion and get rid of the

“There was a backlash of people who felt focal therapy was inappropriate.”

cancer that way. Ablating the tumor isn't the hard part. The hard part is knowing where the lesion is and targeting it.

Fifteen years ago, we had several hundred radical prostatectomy specimens; a researcher from Japan named Dasako Hirano, who had been with us for two years, outlined the tumors on acetate paper and then we put them into a 3D system so that we could simulate where these tumors were using different biopsying techniques. We showed that if you use the transperineal approach to place a needle into the prostate every five millimeters, you could sample the whole prostate without missing many significant cancers. I felt that it was safe to go forward with targeted focal therapy. We knew we would not do any harm with 3D mapping biopsies.

We also talk about MRI in relation to focal therapy. MRI has been


“Focal therapy is a response to overtreatment.”

around for a long time. We've gone from 1 Tesla to 3 Tesla and now 5 Tesla MRI units. We're getting better at reading the MRI results. There has been a lot of discussion about how accurate MRI is and what it misses. MRIs still can miss aggressive cancers. Depending on which expert you believe, MRI misses anywhere from 7-10% up to 30% of aggressive cancers. MRI is a lot simpler than our painstaking 3D mapping biopsy, though, so it's caught on.

Dr. Mark Emberton was the first to champion MRI in the United Kingdom. Dr. Emberton and his team now have a lot of experience in using MRI in focal therapy, primarily cryotherapy.

“We've got to follow people a long time before we come to a consensus.”

But to me, the gold standard remains the mapping biopsies. MRI is good, but not perfect. Perhaps we can use molecular markers along with MRI to rule out more aggressive cancers.

Focal therapy is a response to overtreatment and it does have a place, but with prostate cancer, we've got to follow people a long time before we come to a consensus. 



Mark Emberton, MD

Focal Therapy



Dr. Mark Emberton is a Professor of Interventional Oncology at University College London.

Prostatepedia spoke with him about focal therapy for prostate cancer.

Why did you become a doctor?

Dr. Mark Emberton: As a schoolboy, it was science and a fascination with that subject that took me to it. I attended school in the UK where I stayed with a family friend who was a pharmacist. I used to help him on Saturdays. Because it was quite rural, he treated minor injuries and stuff like that. I think that fixing up people's cuts and bruises was as close as I got to it.

My parents lived in San Diego, California, so I nearly went to medical school in America, but I went to school in London and loved it. I wasn't a particularly bright student, but medicine suited me, and I did well at it. Then I ended up in one of the largest medical schools in the country doing focal therapy.

What is focal therapy for prostate cancer?

Dr. Emberton: Focal therapy is an attempt to improve the therapeutic ratio. It addresses the harms and benefits of treatment. In prostate cancer treatment, the harms are too great for the benefit to accrue.



"Focal therapy is an attempt to improve the therapeutic ratio."



We can't improve the benefit very much, but we can certainly reduce the harms that we inflict on our patients. Nearly every patient who has been treated for prostate cancer will experience a reduction in quality of life because of the impact on his sexual function, continence, or rectal function.

Focal therapy attempts to address that by preserving tissue. We've managed to preserve tissue in all other cancer management: breast through lumpectomy, kidney through partial nephrectomy, liver through partial hepatectomy, and penile cancer through partial penectomy. Prostate is the last bastion. Until recently, all men had the prostatic equivalent of bilateral mastectomy. In other words, their whole prostate tissue was removed irrespective of tumor volume, location, or number. Everyone was treated the same. With focal therapy, we attempt to preserve tissue, which preserves function.

How do doctors determine if focal therapy is appropriate for a man?

Dr. Emberton: It's not for everybody. At the moment, we do surveillance so that men with very low-risk disease have no treatment. We offer surgery to men with high-risk disease who've got extensive, high-burden tumors in the same way we manage, say, breast cancer. We might choose to watch an elderly woman with a small breast lump. We might choose to do a mastectomy on a young woman with very aggressive breast cancer. But the majority of women—currently 80%—can get away with a lumpectomy. This is enabled by the ability to identify tumors and determine location and volume.

That's a very recent development in prostate cancer. Until very recently, we were treating all men blindly. Since Hugh Hampton Young did his first prostatectomy at Johns Hopkins about 100 years ago, we've been treating prostate cancer without knowledge of tumor location.

What is the role of imaging?

Dr. Emberton: The new trick in town is that we can see the prostate cancer with MRI. If we can see it, we can direct needles at it. If we

can direct needles at it, we can direct energy at it. We can zap the tumor rather than having to remove the whole prostate. We can have a much more nuanced approach now. Instead of treating all men the same, we can now stratify men by risk with great precision by biopsying them differently depending on where the tumor is and then allocating treatment depending on the risk stratification that has been assessed.

If a man has one millimeter of Gleason 4+3, most of us would not treat. I certainly wouldn't. If he has extensive bilateral disease, I would offer whole-gland treatment in the form of surgery or radiation therapy. If he has got a 0.5 cc tumor in the right peripheral zone of the prostate, I see no reason why we shouldn't offer a selective destruction of that tumor that preserves erections, ejaculation, and continence. We're doing that today. We're having conversations with men today that we couldn't have had three to four years ago because we didn't have the tools.

What about other advances in imaging?

Dr. Emberton: PSMA is very useful in staging men. It's concordant with MRI and the prostate, but it doesn't give us the spatial resolution that we would require to decide which part of the prostate to treat. The PSMA PET/CT will be positive on the left or the right side of the prostate, but will not give us any more information. It's really useful in the high-risk man with whom you're trying to rule out metastatic disease.

There are a variety of forms of focal therapy; correct?

Dr. Emberton: I think conceptually, it's very clear. We offer men focal therapy when we can treat the tumor plus a margin and we think we can

do so faithfully. But there are lots of ways to do it. Just like surgery, you can have an open, transperineal, laparoscopic, or robotic prostatectomy. In brachytherapy, high-dose rate (HDR), low-dose rate (LDR), CyberKnife, TrueBeam, protons, external beam, the principle is the same.

Yes, we have a few options with focal therapy, though not as many as surgeons and radiation therapists. We're often accused of having a cornucopia of ways of treating. Actually, we don't. We have heat (hot or cold) and we have electricity in the form of radio frequency or electroporation.

You mentioned a decrease in erectile dysfunction (ED) and incontinence with focal therapy. How dramatic is that decrease?

Dr. Emberton: With focal therapy, we can get rid of incontinence. Obviously, there is no such thing as zero in medicine, but I would say incontinence pads are required in one in 200-300, which is similar to TURP. Actually, it's less than TURP because we don't breach the bladder neck. In the two trials that we've published, 90-95% of men kept erections sufficient for penetration when we treated half the prostate. A third of the men required some Viagra (sildenafil).

Now, in the second cohort, some men were already on Viagra (sildenafil). We didn't exclude them. These were men in their 60s and 70s, so their erections were fading. So, it's not just a bit of a difference between surgery and radiation therapy—it's dramatically different. Men expect to keep their erections after focal therapy. Some say that their ejaculations are not as strong as they used to be. Those are the kinds of discussions we're having because they expect

to keep their erections. If that's all we're worried about, I'm happy.

Is all of that related to who was having problems before treatment?

Dr. Emberton: No, the ejaculatory ducts are a midline structure. If you treat in the midline, you destroy them. The prostate makes semen. The more prostate you treat, the more semen you will stop making. If you treat off the midline, you won't affect the ejaculation much. They'll always have some reduction because you're interfering with semen production.

I suppose anytime you have any sort of treatment, there will be some impact, right?

Dr. Emberton: Yes. We are destroying tissue. I don't have a magic wand. Yes, I tell everybody they will experience a slight reduction in ejaculatory volume. By age 60 or 70, most men have already lost quite a bit of volume.

Men start to lose a bit of volume in their 40s or 50s; treatment affects that. Biopsy also affects that, so extensive biopsies can result in men losing ejaculate, presuming the ducts are affected. Focal therapy also averts the loss of penile length associated with hormones in radiation therapy and surgery. It's not that well known. Many men go into surgery not knowing about penile shortening.

What role does salvage focal therapy play?

Dr. Emberton: For many reasons, it's one of the most challenging treatments we do with the most challenging patients we have. They're very disappointed that their initial treatment failed. They're also at very high risk of having metastatic disease. Typically, focal therapy is done in men who've had radiation therapy. I don't see many men who have radiotherapy after surgery.





“The new trick in town is that we can see the prostate cancer with MRI.”



Men who fail after radiation therapy have focal ablative therapy usually.

Radiation-recurrent disease tends to be very focal. There is usually one part of the prostate that evades the radiation therapy—not always, but it’s been described in many papers. We stage them very carefully.

The first thing I do is an MRI of the prostate: Can I see it? With PSMA PET, has it spread beyond the prostate? If the answers are yes and no to those respective questions, then they get a targeted biopsy of the lesion to prove what it is. It’s not unusual to find high-grade disease there in this case.

Then we offer treatment, usually using high-intensity focused ultrasound (HIFU), cryotherapy, extreme heat, extreme temperature, or electricity. The results are the same whatever you do. These men have about 50% freedom from progression at five years. It looks as though you cure about half, which is not a lot. They’re all destined to progress if you don’t do anything. They’ve all gone to hormones, which do not cure anybody. A well-selected man has between 40-60% freedom from progression at five years, which is probably a cure.

Those aren’t bad odds, but the risk is incontinence. With planning treatment, we’re much better at predicting that. Incontinence and rectal damage are very rare now with focal salvage.

Wouldn’t some of these men already be suffering from the side effects of a primary treatment?

Dr. Emberton: Yes. They usually have rectal problems, impotence, and a very stiff prostate, so it’s quite easy to make them incontinent. They’ve got a sphincter that’s rock-solid. Sometimes it’s almost impossible to get the needles into the prostate.

Why is focal therapy so controversial?

Dr. Emberton: Good question. Philosophically, if you’re willing to engage in active surveillance, you should be willing to engage in focal therapy.

Let me play this out. In active surveillance, you determine whether a man has disease above a certain threshold of risk: if above, you treat; if below, you don’t.

Focal therapy is the same, but instead of making a judgment at the patient level, we’re making it at the prostate level. We look at the prostate very carefully. If there is any disease there that I’m not happy with, say in the corner there is a nasty Gleason 4+3, we treat it and are happy to observe the rest of the prostate. It’s exactly the same decision-making process in active surveillance, but we apply that decision to the prostate rather than to the patient.

Is focal therapy more commonplace in areas where MRI is more commonplace?

Dr. Emberton: Yes. You can’t do it without MRI.

Can American patients go to the UK to get an MRI?

Dr. Emberton: Sure. Fly on over business class, get an MRI, and still



have money left over! Not quite. MRIs are quite expensive in the US. They’re about \$3,000. In the UK, MRIs are about \$1,000. In Spain, about \$600. There are some places in Florida where they do an MRI for about \$600.

In the United States, many places do great MRI: New York University, Cornell, University of California, Los Angeles, and University of Southern California. Most decent places in the United States offer MRI.

Probably not at the community level, but people could travel to these larger centers, I suppose?

Dr. Emberton: Actually, the community physicians I’ve met in big urology practices are commercially astute and know what patients want. Many of them—Chesapeake Bay Urology, for example—offer high-quality MRI. They partner with radiology to offer men really excellent service. I’m impressed that once Americans decide to do something, they can do it very quickly, much quicker than we can with our National Health Service and government-driven healthcare. I think we’re going to see change quickly in the US now.

Do you have any other thoughts for men considering focal therapy?

Dr. Emberton: Men should insist that before their urologist puts a needle in their prostate, they find out where the tumor is. Demand imaging first. I think that’s by far the most important thing. Focal therapy follows once you’ve been properly risk-stratified. By far, the most important thing is that men just put up their hand and say: “No, I want some decent imaging first, thank you very much.” This is a human rights issue. ^{PP1}



Behfar Ehdaie, MD

Focal Therapy + Partial-Gland Ablation



Dr. Behfar Ehdaie is a urologist at Memorial Sloan Kettering Cancer Center in New York City.

Prostatepedia spoke with him recently about focal therapy and laser ablation.

Why did you become a doctor?

Dr. Behfar Ehdaie: I initially was exposed to medicine in dealing with some of the medical challenges that my mother faced related to cancer. It made a very large impression on me to see how my mother interacted with her physicians and how she was comforted by so many of them. To be able to give back and to provide comfort to other people with regard to different diseases was very important in my decision to be a doctor.

On top of that, being an effective and good physician were challenges that I found to be stimulating.

What is partial-gland ablation versus focal therapy?

Dr. Ehdaie: I think we've come to a point in prostate cancer management and treatment in which these distinctions and terminology are becoming more important. As you know, over the past three decades, we have developed proven effective whole-gland treatments for the

prostate that include radical surgery and radiation therapy. A less invasive form of prostate cancer treatment must involve less than total treatment of the whole gland. Therefore, the term *partial gland* has evolved. We use the word *ablation* to suggest that an area of the prostate will be treated, whether that's through heating or freezing or other mechanisms to cause cell death and necrosis.



"We lack both short-term reproducible data and long-term data."



The term *focal therapy* adds a second dimension to partial-gland ablation. This is a general term to refer to any treatment that offers less than whole-gland treatment for prostate cancer. Focal therapy specifically focuses on an image-guided treatment approach, meaning an area that is visualized is specifically targeted and treated. In partial-gland ablation, we use our current abilities to map the prostate to determine which region is most likely to be involved with cancer; we not only seek to treat that area but also to achieve a margin that

may not be visualized on imaging. Focal therapy adds the dimension of image guidance to the armament of prostate cancer treatment, which is more relevant now given that our approach to diagnosing prostate cancer has also evolved over the past decade. We have moved from systematic biopsies to adding biopsies in which we target areas that are first visualized using advanced imaging like multiparametric MRI.

Are you primarily doing focal therapy or partial-gland ablation now?

Dr. Ehdaie: In our different studies and trials, we have different forms of treatment. Specifically, in studies in which we define the area of treatment by MRI, we term those treatments focal therapy. We currently have a clinical trial looking at MR-guided high-intensity focused ultrasound (HIFU) that we perform in the MRI suite.

We also have two other clinical trials in which we direct our treatment to a region predominantly defined by the biopsy criteria, in which the imaging is an addition to the tools we have used to define where we want to treat. We currently are performing both focal therapy and partial-gland ablation on patients based on the modalities that they would be eligible for.

How do we know which patients are appropriate for either focal therapy or partial-gland ablation?

Dr. Ehdaie: I think ultimately we can make the distinction between patients who need radical surgery or radiation treatment and those patients who need less invasive forms of treatment that we would term partial-gland ablation specifically, without making the distinction with focal therapy to answer this question.

Currently, I believe eligible patients are those who have an intermediate-risk prostate cancer defined as Gleason grade 3+4, or in some cases very low-volume Gleason 4+3 prostate cancer defined by prostate needle biopsy and confirmed with a secondary imaging test to rule out other areas of intermediate-risk



"I do not believe partial-gland ablation or focal therapy should replace active surveillance."



prostate cancer. Those patients may have other areas of low-grade, low-risk prostate cancer, specifically Gleason 3+3, which would go untreated and be monitored as they currently are in many active surveillance cohorts.

I do not believe focal therapy or partial-gland ablation in its current form should be evaluated or used in patients with high-risk prostate cancer; that includes men with Gleason 4+4 or higher, high-volume Gleason 4+3, with imaging characteristics suggesting bilateral intermediate-

or high-risk disease, or disease that has escaped the prostate, including locally advanced prostate cancer or prostate cancer that has metastasized to the lymph nodes or the bone.

Could low-risk patients just as easily choose active surveillance? Is it just patient choice: active surveillance or partial-gland ablation?

Dr. Ehdaie: I think active surveillance, partial-gland ablation, or focal therapy, and whole-gland treatments, which include radical retropubic prostatectomy or radiation therapy, exist on a spectrum for disease management in prostate cancer.

I do believe that there are patients who we would all agree are very good candidates for active surveillance. Men who've been diagnosed with Gleason 3+3 prostate cancer fall into this category. I think our discussion about men who may be eligible for focal therapy or partial-gland ablation would include men with intermediate-risk prostate or Gleason 3+4 or 4+3 prostate cancer.

Of course, some of the men with low-volume Gleason 3+4 prostate cancer in foci within the prostate gland would also be considered very good candidates for active surveillance. It's important that all patients are offered all treatments and that those treatments are explained in detail at every consultation.

"How often does cancer recur after partial-gland ablation and focal therapy?"

Dr. Ehdaie: As we accumulate more data, it's important to make a distinction that partial-gland ablation and focal therapy are treatments that are currently best evaluated within the setting of clinical trials. That suggests that the majority of the data on focal

therapy and partial-gland ablation are still evolving, specifically long-term data.

To specifically answer your question, I think we have to define what is treatment failure or recurrence. In focal therapy and partial-gland ablation, the definitions can be divided into the following: 1) recurrence of cancer or residual cancer in the area targeted for ablation; 2) intermediate- or high-risk cancer diagnosed in an area or lesion that was never targeted for ablation; 3) or patients who present with extensive disease after focal therapy, suggesting that there is cancer outside of the prostate gland.

When we look at studies evaluating short-term outcomes in partial-gland ablation, the distinctions are very critical.

Currently, we haven't specifically defined any of those endpoints. Current studies look at multiple ablation modalities—freezing or heating the tissue or using other measures to achieve necrosis or cell death. We think, and it has been reported, that in approximately 80-90% of patients we can classify risk appropriately to define whether a patient has a single focus of intermediate-risk prostate cancer with no other areas of intermediate-risk or higher-risk cancer somewhere else in the prostate.

Are some modalities of targeted ablation more effective than others?

Dr. Ehdaie: Those numbers continue to vary and continue to improve when we add more components or better imaging to our treatments. We currently have two studies that have not yet reported or achieved their endpoint. We are not able to report our outcomes of local recurrence, out-of-field recurrence, and overall delay in radical treatment, but these are the outcomes we are following.



*What if a man's cancer does come back?
Are salvage therapies more difficult
if the man has had focal therapy?*

Dr. Ehdaie: I think the difficulty of subsequent salvage therapies depends on how much of the prostate gland was treated with different techniques in partial-gland ablation. In addition, I think the source or type of ablation that was conducted provides



*“We’re still learning
more about the role
of genomics.”*



different levels of complexity for returning to subsequent radical surgery or radiation treatment. However, we think in general the salvage treatments after partial-gland ablation should have less complexity than after whole-gland treatments in prostate cancer.

Is focal therapy controversial? Why?

Dr. Ehdaie: I don't think *controversial* is the right word to use in regard to focal therapy or partial-gland ablation. I think a better way to term our current state in accepting focal therapy and partial-gland ablation is that we lack both short-term reproducible data and long-term data. Many are amenable to studying focal therapy and partial-gland ablation to determine those outcomes.

You're saying it's not that focal therapy is controversial; it's just that we don't have enough data yet?

Dr. Ehdaie: Absolutely. That's something that's currently undergoing review. There are many studies looking at all those outcomes, including studies done at our center.




And you think patients should seek focal therapy through a clinical trial?

Dr. Ehdaie: At some level, a clinical trial or a registry in which the goals of treatment, follow-up, and subsequent steps are defined prior to treatment are the ideal environments in which to offer patients partial-gland ablation or focal therapy.

Is there anything else you think patients should know?

Dr. Ehdaie: The most important aspect of partial-gland ablation is patient selection. The most important component of patient selection is going to experienced physicians at centers that practice all modalities of treatment in prostate cancer with developed prostate cancer programs that address all barriers and needs in prostate cancer management. I do not believe partial-gland ablation or focal therapy should replace active surveillance. I also believe that follow-up after partial-gland ablation is critical and will include both imaging and biopsies.

What do you think the role of genomics will be in vetting patients for focal therapy?

Dr. Ehdaie: I think we're still learning more about the role of genomics in patient selection. I don't believe that genomics will have a role in following patients after partial-gland ablation, but it will contribute more to patient selection. 



R. Jeffrey Karnes, MD

Salvage Focal Therapy



Dr. R. Jeffrey Karnes is an Associate Professor and Vice Chair of the Urology Department at the Mayo Clinic in Rochester, Minnesota.

Prostatepedia spoke with him about salvage focal therapy for recurrent prostate cancer.

Why did you become a doctor?

Dr. Jeffrey Karnes: Some doctors are from a legacy: somebody in their family has been a physician. My parents are both schoolteachers. I think there is an element of being able to give something back to students, in their situation, and to patients, in mine. In that same vein, though, I'm an academic, so I do have students. I have residents and fellows. Both my parents really gave of themselves in terms of time and even material things to those less fortunate.

I enjoy the personal interactions and also like results quicker, and for the latter, this is probably one of the reasons I like the surgical field. I still like the mix of the intellectual portion of my job with the physical or surgical portion. Plus, I like complex problem-solving, so I enjoy the challenging cases.

My undergraduate degree is in international politics from Brown University. I didn't necessarily want

"There is more at risk with focal salvage therapy."

to study the pre-med curriculum (i.e., math and science) because I knew that I'd have to repeat all that in medical school. I decided to do something that also interested me. I was completely ignorant of any international politics.

So you studied political science, but did all the necessary pre-med work?

Dr. Karnes: I did. I don't know what would have happened if I hadn't been admitted to medical school. I don't think I would have been a politician.

What is focal therapy?

Dr. Karnes: Focal therapy is partial treatment of the prostate gland as opposed to whole-gland treatment (i.e., radical prostatectomy, brachytherapy, and photon or proton radiation therapy).

How did focal therapy even become in vogue? To abate some of the potential side effects of whole-gland treatment. It is exciting and promising, yet remains investigational.

Isn't a focal approach common in other kinds of cancers?

Dr. Karnes: It can be. The most common is probably breast cancer. I'm far from an expert in breast cancer, but recurrence rates can be higher with focal therapy, meaning a lumpectomy or quadrantectomy, where a quadrant of the breast is removed. But, the survival has been similar between partial- vs. whole-breast treatment.

Why not the prostate? I would say that focal therapy, in general, hasn't risen to the forefront in the United States or internationally.

There are a couple of limitations for focal therapy in general:

- 1) What do we know about prostate imaging? Prostate cancer is known to be a multifocal cancer within the prostate. The multiparametric MRI is good. It's not perfect. But even if we can identify a small focus of intermediate-grade prostate cancer, are we certain that is truly the disease to treat, as opposed to some scattered higher-grade cancer that may not be showing up on MRI, but hopefully might get picked up on a whole-gland biopsy done along with a targeted biopsy? I think we're getting to

the point where an MRI is pretty good at imaging the entire prostate.

- 2) We still have a second unresolved issue of what constitutes the biological index lesion of the cancer. If we do have multifocality, are we sure exactly which focus to treat? Even some of the well-known researchers in focal therapy (focal cryotherapy, high-intensity focused ultrasound [HIFU]) can still have patients with a fairly high recurrence, or persistence of the cancer after the partial or focal therapy about 20% of the time.

What is salvage focal therapy?

Dr. Karnes: Focal salvage therapy is focal therapy done when a man recurs after primary treatment. There is more at risk with focal salvage therapy. What do I mean by *more at risk*? Obviously, salvage therapy means that there has already been a primary treatment that has failed, so there is even more impetus to get it right the second time around.

For that second time around, if we go back to those two items that I mentioned above (imaging and the biology of the index lesion), there has not been, to my mind, enough research into MRI imaging of recurrent prostate cancer. More research needs to be done into the MRI performance accuracy after a radiation or biochemical failure.

What about some of the newer imaging like gallium-68 PSMA PET/CT?

Dr. Karnes: PET imaging has been good at detecting metastases, but in terms of imaging the primary tumor, the resolution hasn't been the best. Now, we and others are moving into a PET/MRI scan.

"I don't think we know exactly what constitutes a success."

That is a fusion scan?

Dr. Karnes: A fusion scan with MRI rather than the PET/CT. Obviously, an MRI provides more resolution of the prostate. To me, MRI is obviously the gold standard when it comes to imaging the primary prostate. We're certainly using the technology. Others are using it. We don't really know what the exact accuracy is of the MRI/PET fusion scan in those who have had radiation failure.

And, as I mentioned, I don't think we have really much in the way of a clue regarding the biology of this index lesion in radiation-recurrent cancer in the prostate. I think that in the glands of men who recur after radiation, there is probably higher tumor burden compared to the newly diagnosed patient.

A third problem we have when it comes to focal salvage therapy is that I don't think we even have a great definition of what constitutes a potential local recurrence after primary radiation. The Phoenix definition used by the American Society for Radiation Oncology is the nadir (or lowest) PSA plus 2. This definition predicts recurrence, but what it really predicts is *progression*, not necessarily local recurrent disease.

In this country, for many men who fail radiation, the next treatment is hormonal therapy. Hormonal therapy really has only a palliative intent and won't cure anyone of localized radiation-recurrent disease.

We need to do a better job of appropriately diagnosing radiation-failure patients in the first place. What that better job would be, I don't know. I don't think routine biopsies, which have been looked at in the past, are the answer. But perhaps imaging sooner rather than waiting for the Phoenix definition makes sense. Maybe, as you mentioned appropriately, with the newer PET/MRI fusion scans, we can image men sooner to try to detect a local recurrent disease earlier.

That being said, I do a lot of salvage radical prostatectomies, almost one a week. This is unpublished, but I have not seen a big stage migration (less extraprostatic extension and/or nodal metastasis) in the last decade. I still see a lot of patients with radiation failure; they come to their salvage prostatectomy with seminal vesicle invasion and nodal disease. Up to a third of patients will have seminal vesicle invasion and I see nodal involvement in up to 20% at salvage surgery.

Why is that relevant to salvage focal therapy?

Dr. Karnes: A lot of the seminal vesicle invasion is not always evident on MRI. And a lot of these patients don't get routine biopsies of their seminal vesicles. If they undergo a salvage focal therapy, their doctors are obviously going to be missing a significant component of their disease because salvage focal therapy, in my opinion, doesn't work to ablate the seminal vesicles. Obviously, salvage focal therapy can do a job in the gland itself, but in the appendages, such as seminal vesicles, it is hard to get an appropriate ablation of the entire seminal vesicles because of the risk to adjacent structures—the bladder, the ureters, and so forth.

Another thought I have about salvage focal therapy is when we look at other forms of ablation technologies like cryotherapy or HIFU, we've morphed



them from whole-gland to focal and now to focal salvage therapies. But I don't think we even know who the ideal candidate is for whole-gland HIFU or whole-gland cryotherapy let alone the focal form of the therapies in a treatment-naïve patient.

Obviously, these are alternatives or options for patients who are newly diagnosed, but more troubling for me is this: I don't think we know exactly what constitutes a success. How do we monitor whole-gland cryotherapy or whole-gland HIFU? We've used PSA failure as a definition, but are we really using the right tool to monitor?

The current approach is monitoring the PSA along with periodic imaging?

Dr. Karnes: Essentially, yes. As I mentioned, we also use the Phoenix definition. It is a good definition, but once again a definition of progression, but not necessarily a local recurrence. For these ablative technologies, even for whole-gland, we don't know if that fits.

Why would anyone choose focal salvage therapy to begin with? Why wouldn't you go for a more directed approach right away? Is it just about avoiding certain side effects?

Dr. Karnes: Having been a salvage surgeon for a number of years, I think we need to make our salvage therapies better.

Salvage prostatectomy can be a challenging operation: there may not be collateral damage during the surgery, but the healing process is certainly impeded by the previous radiation. There are definitely much higher rates of incontinence in salvage prostatectomy. There are much higher rates of stricture or contracture formation between the urethra and the bladder. Obviously, if we also look at

salvage radiation for radiation failures, we're also adding radiation toxicities. With the whole-gland cryotherapy and HIFU as a salvage therapy, we've even seen a lot of toxicities related to fistulae between the prostate and the rectum. I may be a little bit jaded because I don't see the successes, I only get referred the failures for salvage whole-gland therapies.

In terms of focal therapy, one of the larger groups in the university system in London looked at salvage focal HIFU. They obviously have a wealth of experience with focal therapy and have just expanded that to the salvage setting. They've reported on their complications and their results. But they have only looked at men three years posttreatment, so not a long-term follow-up yet.

Truly, there is an impetus for salvage focal therapies predominately related to the side effects of whole-gland treatments, whether it's salvage prostatectomy, whole-gland cryotherapy, or whole-gland HIFU after radiation failures. The side-effect profile is certainly heightened during those treatments.

Those side effects can be devastating for men.

Dr. Karnes: Absolutely. With salvage prostatectomy, there is always a potential chance for an artificial sphincter. It's a little more challenging if there are issues related to strictures and/or fistulae.

Certainly, these salvage therapies need to be done in centers of excellence. In parallel with focal salvage therapy research, we need to work at making our focal and salvage therapies better. That may be developing a better strategy of following irradiated patients, especially younger men with a long life expectancy.

Do you think advances in salvage whole-gland therapy will happen in step with advances in imaging? The better we can see where the cancer is, the better we'll be able to safely remove it?

Dr. Karnes: I do. Better ability to image, to understand the biology of the primary tumors, and perhaps even incorporate genomics, may allow us to better select patients for focal therapy in general and for salvage focal therapy specifically.

But for now, is focal salvage therapy too experimental to be safe for most patients?

Dr. Karnes: Salvage focal therapy should be considered investigational. It should be done in a center of prostate cancer excellence and, I believe, as part of a research protocol.


As part of a clinical trial?

Dr. Karnes: Yes, a clinical trial or a clinical investigation (prospective data collection).

What do we do for patients who perhaps fail a focal salvage approach? Are they salvageable after that?

Dr. Karnes: For the most part, I think they are, but the ante just got raised. In my experience, the more treatments you have failed, the more likely complications of your following treatment.

At that point, that man has been through the wringer.

Dr. Karnes: Yes. I've treated a lot of patients with primary radiation failure. Each time we add some level of treatment after the radiation failure, whether it's brachytherapy, whole-gland cryotherapy, or whole-gland HIFU, our ability to successfully salvage the patient becomes more complex. We need to try and get it right the first time around. 



Clinical Trial: Paul Cathcart, MD Robotic Prostatectomy After Focal Therapy

Dr. Paul Cathcart is a consultant urological surgeon at Guy's Hospital and St. Thomas' Hospital in London.

Prostatepedia spoke with him about a clinical trial he's running that looks at robotic surgery in men whose prostate cancers have come back after focal therapy.

Why did you become a doctor?

Dr. Paul Cathcart: I always liked science; that was my favorite subject. I was thinking about whether to become a vet or a doctor and did lots of school visits. During one of those visits, I met an inspirational character, a surgeon. I spent some time with him, following him around hospital wards and clinics. I thought that he was the sort of person I would like to be: he does the job I'd like to do. I think that's often the case in life: you meet some inspirational figure who pushes you along one line.

Later on, another inspirational figure who came into my life was a urologist. I was originally going to be a colorectal surgeon. Everything was set for that. Then I met this urologist who showed me the different mix there is in urology, which I found interesting.

Then I met Dr. Mark Emberton; I was his research fellow for many years.

He's quite an inspirational person as well. I've been working with him for 17 years now on various things.

What is the thinking behind your trial on robotic surgery after focal ablation?

Dr. Cathcart: Focal therapy is a new concept, which Dr. Emberton and one or two other people have pioneered to reduce the side effects and morbidity of prostate cancer treatment. Unfortunately, a proportion of these patients will experience recurrent disease after focal therapy. No cancer treatment is 100% effective. A couple of these focal therapy patients were recurring three or four years after starting the focal therapy program.

No urologist wanted to operate on these patients because they felt that it would be an extremely difficult surgery. In fact, urologists were only offering exenterations to remove the patients' prostate, bladder, etc.

I got to know quite a few of these patients. (I do a lot of post-radiotherapy surgery, as well.) I decided that this procedure called *salvage surgery* interested me. We thought that we could do this salvage surgery and maintain good outcomes for our patients because only part of their prostate had been treated during focal therapy. We thought that the

side effects of the surgery after focal therapy would actually be a lot less than after radiation, but we needed evidence to prove it. That is why we set up the trial.

We're also interested in learning why some patients may fail focal therapy. What is it about their disease which leads it to recur? If we can understand why some patients may fail focal therapy, this can help us select up front which patients should have focal therapy and which should not.

What can patients expect to happen during the trial?

Dr. Cathcart: We are halfway through the study at the moment.

Of course, patients undergo a salvage prostatectomy. We take the tissue to be analyzed and look for various genetic markers to see why their cancer may have returned.

This is also a toxicity and side effect study. We have patient-reported outcome measures at baseline and sequentially thereafter. There are a number of blood tests looking at hormone profiles before and after the surgery.

We follow patients for about 12 months after those sequential

patient-reported outcome measures; we're looking to chart that toxicity.

I've taken out more prostates after focal therapy than most because of my link with Dr. Emberton. We're now demonstrating the feasibility and toxicity of salvage focal surgery and trying to understand why these tumors have recurred.

Are you still recruiting patients?

Dr. Cathcart: About 20 patients have undergone the surgery. We're recruiting 20 more. We haven't had any adverse events. We were worried about things like rectal injuries because the rectum can stick to the prostate after focal therapy. We haven't had any of those.

We've actually had a fantastic continence outcome. The prostate cancer community said everyone would be incontinent and impotent, but all our patients so far have been continent. We've got the patient-reported outcome measures to demonstrate it.

The potency rates are taking a little bit longer to return to baseline. The outcomes from potency won't be as good as the continence outcomes. We haven't had any side effects at the time of surgery. No complications or anything, so we're delighted with the way things have gone.

Does the fact that the man has had focal therapy make the potency issues worse?

Dr. Cathcart: It depends on the location of their focal treatment. In those with anterior tumors (tumors away from the neurovascular bundles), we've noticed potency returns faster. If they've had an ablation on the peripheral zone, near where one of the nerve bundles is located, potency returns more slowly.

We're also noticing a difference between different treatments. You can give focal therapy with high-intensity focused ultrasound (HIFU), cryotherapy, or something called electroporation. The different energy sources have different effects on the structures surrounding the prostate and a different impact on the chance of potency returning. Electroporation seems to be very precise and leaves the least amount of collateral damage. In those patients, potency returns faster. Cryotherapy creates more periprostatic fibrosis and scarring; potency takes slightly longer for those patients to return. Potency return for HIFU patients falls somewhere in the middle of the modalities.

I've also taken out prostates after photodynamic therapy. Photodynamic therapy is better relative to preserving the tissue planes, but it does depend on which part of the prostate has been ablated in the first place.

Is there anything else you think patients should know about your trial?

Dr. Cathcart: We're going to get a great understanding of why these patients in particular failed focal therapy. The genetic markers and the locations of the tumors will inform which patients are suitable for focal therapy from the beginning. There may be parts of the prostate, or particular types of tumors or genetic markers, which will identify patients best suited to a whole-gland approach such as a radical prostatectomy up front. It's not just about the location and grade of the tumor, but also about the tumor's genetic signature, which may predispose a particular tumor to being better suited for focal therapy.

It's interesting, in some patients you knock out one tumor say on the right-hand side and that's it, the tumor never comes back.

Other patients' prostates seem somewhat unstable and have multiple tumors that keep appearing throughout the prostate. I'm sure there is a genetic basis to it.

Because we're taking out these patients' prostates, we can analyze all the different tumors. Some people even think that by treating part of the prostate we may be changing the genetics of that tumor—i.e., it gets angrier. I don't think that's the case. This study will help prove that point.

We're also going to open up a comparative arm of the study very soon for patients who have had whole-gland radiation or ablation techniques—open to anyone who has had the whole of their prostate treated with brachytherapy, radiotherapy, HIFU, or cryotherapy. We've been finding that patients who have had surgery following focal therapy have better outcomes than those who have had whole-gland therapy up front. We're going to recruit into that second arm to demonstrate that surgery after focal therapy has a better outcome.

Can non-UK residents come to you for surgery?

I've got a clinic called the Recurrent Prostate Cancer Clinic. I have a reasonable number of patients who come from the United States. They normally come to Dr. Emberton for focal therapy, then if they develop recurrent disease, I operate on them. A lot of urologists wouldn't operate on these patients. Certainly, in the United States, hardly anyone operates on post-HIFU patients simply because HIFU has not been available until very recently. ^{Pd}



Ethan Basch, MD, MSc, FASCO Online Tools

Dr. Ethan Basch is a Professor of Medicine at the University of North Carolina Lineberger Comprehensive Cancer Center.

Prostatepedia spoke with him about having patients report symptoms via web-based portal.

Why did you become a doctor? What is it about patient care that attracts you?

Dr. Ethan Basch: I became a doctor because I like people and value direct service. Patient care is rewarding when I feel I can help people by providing medical knowledge that helps them make decisions, listening, and providing support and compassion, and by connecting them to other professionals or resources that can help them during difficult moments.

Do patients commonly report the majority of cancer treatment side effects to their doctors? What are some of the obstacles to those conversations?

Dr. Basch: Studies show that clinicians (doctors and nurses) are unaware of up to half of their patients' symptoms. The reasons for this are complex. Between clinic visits, patients may be reluctant to call the office with problems or have difficulties getting through. At visits, clinicians might not ask about specific symptoms

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"The reasons for this are complex."

amidst other pressing discussion topics. There are also interpersonal dynamics that play a role. Patients might not want to "let their doctor down" by admitting to difficulties. Similarly, doctors might downplay patients' problems because they are emphasizing positive rather than negative aspects of treatment. Electronic questionnaires bypass these various barriers. They enable patients to respond honestly to straightforward and systematic questions about issues they experience. This information is then conveyed automatically to clinicians.

How are doctors currently using newer technologies—like web-based portals or mobile apps—to make it easier for patients to communicate with them?

Dr. Basch: An increasing number of patient portal systems used by hospitals and clinics enable patients to self-report problems they experience. Clinicians can respond to patients within their usual workflow. There are also a



growing number of mobile apps to facilitate this communication between patients and clinicians. These systems lower the barriers to reaching clinicians and facilitate better communication during and between visits.

Can you tell us about your study that looked at having patients use a web-based portal to report side effects?

Dr. Basch: We conducted a study asking a simple question: If we provide an online system for patients to report symptoms to their doctors and nurses during cancer treatment, will that

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"Between clinic visits, patients may be reluctant to call the office with problems."

improve outcomes? The answer was a resounding yes. In this study, we randomly assigned 766 patients to either usual care or to self-reporting common symptoms on a weekly basis from home or clinic with automated email alerts sent to nurses for severe or worsening

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"It is important to reach out to your care team when you have symptoms."

problems. We found that compared to usual care, the patients who self-reported had significantly fewer emergency room visits, better quality of life, and were able to remain on chemotherapy longer because their symptoms were better controlled. These findings together likely account for the most striking finding of the study, that the median overall survival was five months longer among those who self-reported.

Do you think such web-based portals can help doctors address side effects faster and more effectively?

Dr. Basch: Yes.

Are there any financial implications for reporting side effects electronically?

Dr. Basch: We found a significant decrease in emergency room visits when symptoms are managed through proactive electronic symptom monitoring, which is a potential cost savings.

Do you think patients are more likely to report certain side effects if given the opportunity to do so electronically than if they have to report them during an office visit?

Dr. Basch: Yes, this has been shown in prior scientific studies. Patients are more likely to disclose symptom information through questionnaires than in face-to-face discussions. This is likely due to some of the reasons I mention above.

Is there anything else you'd like patients to know about your study or its implications?

Dr. Basch: It is important to reach out to your care team when you have symptoms.


If you were to do the study again, would you make any changes to the way you had patients report side effects—e.g., mobile app versus desktop portal versus text or newer apps/etc.?

Dr. Basch: We started this study more than a decade ago, and there have been substantial advances since then in health information technology and in patient/clinician familiarity with electronic tools. Today, we use newer approaches, including automated telephone systems and downloadable

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"Bots are on the horizon that will automatically elicit symptoms from patients."

apps. Bots are on the horizon that will automatically elicit symptoms from patients and give advice, and wearable activity trackers will be integrated.

Any thoughts for doctors who may be reading this?

Dr. Basch: It is important to monitor patients' symptoms between visits—treatment for most chronic symptomatic conditions, actually. Although there are logistical and workflow challenges associated with integrating patient-reported outcomes into a practice, there are many benefits: improved communication, patient satisfaction, and clinical outcomes. 



Patients Speak:

David Fitch

Getting Focal Therapy



Mr. David Fitch talks to *Prostatepedia* about choosing focal therapy for prostate cancer.

What was your life like before prostate cancer?

Mr. David Fitch: I live by myself. I'm 74. I'm retired. Ever since I quit working, I found it is a lot better to interact with my friends.

I bicycle and swim. I'm more of a cyclist than a swimmer. I cycle almost every day. I'm probably riding 200 to 300 miles a week. I started doing that initially for the social part of it—all my friends are bicycle folks.

Then I got into the VA Palo Alto swimming pool a few years ago and so I've got a lot of VA pals as well. All my exercise basically started as more

of a social thing. That's what was happening before the diagnosis of prostate cancer.

How did you find out that you had prostate cancer?

Mr. Fitch: That was through the VA. The VA in Palo Alto, California, is really good. I've been going there for over

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"All my exercise basically started as more of a social thing."

10 years. I found out through my endocrinologist. I can't say enough nice things about her. She has literally

saved my life at least twice and this was one of those times. She was looking at my PSA over the years. She said: "It's gently rising. It doesn't really rise to the threshold of being something to worry about."

It was around 2.5 for several years before rising to around 3.5 over a period of about four to five years. She said, "Would you like to go talk to the urology department?" I said, "Sure, I'm always happy to talk to people." She sent me to the head of the urology department.

I had no clue about what a urologist did. I went to see the guy, and he did a digital rectal exam (DRE) and said he could feel a lump. My previous DRE was 18 months earlier with my primary care physician and she said everything was fine.

The urologist sent me for an MRI—I had no idea what an MRI was. This started my research: What's an MRI?

With the MRI he said, "It looks to me like there's something wrong, so I need to do a biopsy."

He told me that the protocol for the VA is a blind biopsy, not using the MRI, just poking 12 holes or so into my prostate and taking samples. Very hit-or-miss. My research indicated that using the MRI fused to a picture of my prostate gave the radiologist a better chance of seeing the suspicious areas to sample, but the VA doesn't do that. There is a program, Veteran's Choice, that allows patients to be sent outside the VA if a procedure cannot be performed within the VA. I was sent to Stanford for an MRI-ultrasound fusion biopsy.

The Stanford radiologist, Dr. Sonn, found lesions on both sides of my prostate. The right side had more suspicious areas than the left. The pathologist's report confirmed the presence of intermediate prostate cancer. On the right side were two areas: Gleason 4+3 and 3+4. On the left side, it was Gleason 3+4.

What was your reaction? How did you feel when you found this out?

Mr. Fitch: I was very concerned of course but not distraught. The VA Urology Department did not inform me of the difference between blind biopsy and directed biopsy or of the availability of the Veteran's Choice Program until I asked. I was now suspicious: What else hadn't I been told? The only solution was my own research. I went down this rabbit hole trying to answer: What is prostate cancer? What does it mean? What do all these numbers mean? Who can do what, and how do I go about finding out? I joined

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"I went down this rabbit hole trying to answer: What is prostate cancer? What does it mean?"

a support group at the VA Palo Alto, which was worthless. Then I went to two other local support groups, one in Los Gatos, and another at Mountain View—both of them pretty good.

I found out from talking to a lot of guys that doctors generally prescribe their own methods of taking care of this stuff, whether or not it fits. Urologists want to cut and radiologists want to radiate. Then I found an online support group, Inspire.com, a partner of Us TOO. It's fairly comprehensive. You can get a lot of questions answered, and you can spend literally hundreds or thousands of hours digging through—it's like trying to take a drink out of a fire hydrant.

I was willing to educate myself. I was looking for people who could help me educate myself to find out what needed to be done. The best way I can characterize this is the problem that I had didn't seem to me to be life-threatening at the moment. It seemed to me like I had plenty of time to figure out what to do next, but I was going to have to do something.

I didn't like the fact that the head of the VA Urology Department told me he could only offer me surgery or radiation—nothing else. I thought both of those things were like amputating my arm because I got a scratch. I told him that. I said, "You're not helping me a whole lot." I had a 20-minute appointment at

most. He just seemed too busy to have any sort of a long conversation. I went in there with all this reference material, a ton of it. I didn't exactly know where I wanted to go with it, but I wanted to have a conversation with the man. His bedside manner was terrible. He gave me 20 minutes and said, "Okay, well, do whatever you want." I wasn't getting anywhere.

At that point, I felt that the VA Urology Department was not very helpful. I began to realize that there is a huge difference in doctors' expertise as far as prostate cancer was concerned. I realized that I had to take this into my own hands. I had to educate myself in order to be able to go forward: What is a urologist? A radiologist? An oncologist? Do they specialize in prostate cancer?

Later, after my focal laser ablation (FLA) procedure, I met Dr. John Leppert, a VA urologist who has been very helpful and supportive in my quest to understand prostate cancer.

Did you turn to the online groups? Is that where you went first for education?

Mr. Fitch: I started online, yes. I did a lot of reading. I just worked for a long time until I had the answers that I wanted. Additionally, I began to hear the names of certain doctors mentioned over and over again: Dr. Snuffy Myers, Dr. Mark Scholz, Dr. Mark Moyad, Dr. Fabio Almeida, Dr. Dan Sperling, Dr. Pete Carroll, Dr. Joe Busch, and many others. In many cases, Google was where my investigation began and I watched many YouTube videos.

I concluded that many doctors want to cut something out of me or to radiate me, and both those things have serious consequences. I didn't like either one.

It was about that time that I stumbled onto FLA. It probably had more to do with side effects than it did with whether it worked or not, quite frankly. I found that the biggest side effect from FLA was financial. It would cost me \$20,000.

I decided not to buy a new car that year and use the money to take care of my body instead. I'm being a little facetious here. If it didn't work, I could always do anything I wanted to the second time around. That's what led me to FLA.

Once you found out about focal therapy as an option, how did you figure out which form of focal therapy was best?

Mr. Fitch: My FLA was done in 2016. There are more types of focal therapies now than in 2015 when I made the decision. Additionally, there are very few doctors who do this particular FLA. I went to Dr. Eric Walser at the University of Texas Medical Branch in Galveston, who I think I found out about on Inspire.com. Initially, I was going to Dr. John Feller at Desert Medical Imaging in Indian Wells, California. He had a clinical trial that I was eligible for, but I changed my mind at the last minute because Dr. Feller's clinical trial would cost more than Dr. Walser's commercial practice and would require two trips. And Dr. Feller uses an MRI machine that is 1.5 Tesla. I know it works just fine in the right hands, but it is not a 3.0 Tesla machine.

What was the actual procedure like for you?

Mr. Fitch: The procedure was outpatient. It lasted maybe an hour. I was never knocked out. It was just local anesthetic. I spent a few days in Galveston recovering.

They did two overlapping ablations on the right side and one on the left.

They took larger margins to preclude missing some hard-to-see cancerous spots. Prior to this time, FLA procedures had recurrence rate in the 10-15% range. Taking a little larger margin around the tumor would reduce the recurrence rate. And in my case, they ablated twice, overlapping, on the right and once on the left side. The tumor on the left side was rather small and hard to see. The two tumors on the right side were fairly close to the urethra, which meant that when my poor old prostate swelled up from the ablation, it closed off the urethra. Without a catheter in place, I wouldn't have been able to pee.

The only painful part of the procedure was reinsertion of the catheter for the blocked urethra. I ended up staying in Galveston from Monday to Friday waiting for the urethra to open. I was told this problem was not typical and was probably due to the ablation near the urethra.

Any side effects after the treatment?

Mr. Fitch: My ejaculations are dry. I'm told that's pretty typical. I'm 74 years old and not having kids is really not a problem for me. Otherwise, there don't seem to be any aftereffects.

How are you monitoring now for potential recurrence after treatment?

Mr. Fitch: Active surveillance. The protocol is to have a PSA test every three months and an MRI at six months and 12 months. If everything is clean at the end of 12 months, then maybe an MRI once a year. It varies a little bit after that. The PSAs typically go on at three-month intervals. They're just part of my normal blood work that I have done at the VA.



To put the PSA in perspective, before the FLA, it was about 3.5. Three months after FLA, it dropped to 2.3. Then at six months, it dropped to 0.25. I was so surprised by that number that I had it confirmed with a second test a few days later. It was 0.28.

At nine months, it jumped back to 0.55. That could have been partly due to riding my bike a lot. That does have an impact on PSA. At one year post-FLA, it is 0.43.

I've had a one-year MRI as well which shows some scarring but no other problems.

Do you have any advice for men who are in a similar situation?

Mr. Fitch: I would do it again for intermediate prostate cancer (i.e., Gleason 7) which has not metastasized. It's expensive, not covered by insurance, and I had to travel, but it was well worth it. No pain, no leaking, and sex works. If the cancer reappears in the gland it can be reablated or any other procedure used. There are many available therapies for organ-contained prostate cancer that has not metastasized: cryotherapy, CyberKnife, MR-guided focused ultrasound, NanoKnife, proton beam, photodynamic therapy with TOOKAD, stereotactic body radiation therapy (SBRT), brachytherapy (seeds), and more. Technological improvements are happening quickly. I suspect we're headed down the road of some new, permanent therapies that will eradicate prostate cancer forever. Immunotherapy comes to mind. Until then, FLA seems like a good interim measure.


Any other thoughts for other men struggling with prostate cancer?

Mr. Fitch: Listen to the doctors. If you like what they say, and if you

want to follow their advice, that's fine. If you think there might be something else out there that works better, at least take a look at other options and see how they stack up against what you're being told. Prostate cancer probably hasn't changed a heck of a lot in a long time, but the ways that we approach it are changing rapidly. Active surveillance for low-risk cancer (Gleason 6) is increasing dramatically, and scanning techniques make this possible.

If it weren't for the new technologies in scanning, we wouldn't be doing focal anything. Scanning helps find the tumors. I was a fighter pilot. If somebody was shooting at me, I could combat that by seeing the threat and defeating it. The same goes here. If you can see it, you can probably defeat it.

There are a lot of scanning techniques including MRI. PET/CT scanning techniques use different imaging agents (injected during the scan) and can help to see both inside and outside the prostate. These agents include C 11-acetate, PSMA, Axumin (fluciclovine F 18), and many others. It's worthwhile investigating those to make sure that a guy knows exactly what he's got and exactly what he has to deal with before he goes down any road. He's got lots of time, especially if it's low or intermediate risk. Take the time to educate yourself, to understand what needs to be done.

The last point I'd make is to attend the Prostate Cancer Research Institute (PCRI) conferences in the fall. It's designed for patients, given by world-class doctors, lasts three days for \$50 or so. The education is remarkable. 

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Who should not take XTANDI?

XTANDI is not for use in women. Do not take XTANDI if you are pregnant or may become pregnant. XTANDI can harm your unborn baby. It is not known if XTANDI is safe and effective in children.

Before you take XTANDI, tell your healthcare provider if you:

- Have a history of seizures, brain injury, stroke or brain tumors.
- Have any other medical conditions.
- Have a partner who is pregnant or may become pregnant. Men who are sexually active with a pregnant woman must use a condom during and for 3 months after treatment with XTANDI. If your sexual partner may become pregnant, a condom and another form of birth control must be used during and for 3 months after treatment. Talk with your healthcare provider if you have questions about birth control. See “Who should not take XTANDI?”
- Take any other medicines, including prescription and over-the-counter medicines, vitamins, and herbal supplements. XTANDI may affect the way other medicines work, and other medicines may affect how XTANDI works. You should not start or stop any medicine before you talk with the healthcare provider that prescribed XTANDI.

How should I take XTANDI?

- XTANDI is four 40 mg capsules taken once daily.
- Take XTANDI exactly as your healthcare provider tells you.
- Take your prescribed dose of XTANDI one time a day, at the same time each day.
- Your healthcare provider may change your dose if needed.
- Do not change or stop taking your prescribed dose of XTANDI without talking with your healthcare provider first.
- XTANDI can be taken with or without food.
- Swallow XTANDI capsules whole. Do not chew, dissolve, or open the capsules.
- If you miss a dose of XTANDI, take your prescribed dose as soon as you remember that day. If you miss

your daily dose, take your prescribed dose at your regular time the next day. Do not take more than your prescribed dose of XTANDI in one day.

- If you take too much XTANDI, call your healthcare provider or go to the nearest emergency room right away. You may have an increased risk of seizure if you take too much XTANDI.

What are the possible side effects of XTANDI?

XTANDI may cause serious side effects including:

- **Seizure.** If you take XTANDI you may be at risk of having a seizure. You should avoid activities where a sudden loss of consciousness could cause serious harm to yourself or others. Tell your healthcare provider right away if you have loss of consciousness or seizure. Your healthcare provider will stop XTANDI if you have a seizure during treatment.
- **Posterior Reversible Encephalopathy Syndrome (PRES).** If you take XTANDI you may be at risk of developing a condition involving the brain called PRES. Tell your healthcare provider right away if you have a seizure or quickly worsening symptoms such as headache, decreased alertness, confusion, reduced eyesight, blurred vision or other visual problems. Your healthcare provider will do a test to check for PRES. Your healthcare provider will stop XTANDI if you develop PRES.

The most common side effects of XTANDI include weakness or feeling more tired than usual, back pain, decreased appetite, constipation, joint pain, diarrhea, hot flashes, upper respiratory tract infection, swelling in your hands, arms, legs, or feet, shortness of breath, muscle and bone pain, weight loss, headache, high blood pressure, dizziness, and a feeling that you or things around you are moving or spinning (vertigo). XTANDI may cause infections, falls and injuries from falls. Tell your healthcare provider if you have signs or symptoms of an infection or if you fall.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of XTANDI. For more information, ask your healthcare provider or pharmacist.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Please see the Brief Summary on the following page and the Full Prescribing Information on XTANDI.com.

**QUESTIONS ABOUT
XTANDI?**

Call 1-855-8XTANDI (1-855-898-2634)

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PATIENT INFORMATION
XTANDI® (ex TAN dee)
(enzalutamide)
capsules

What is XTANDI®?

XTANDI is a prescription medicine used to treat men with prostate cancer that no longer responds to a medical or surgical treatment that lowers testosterone and that has spread to other parts of the body.

It is not known if XTANDI is safe and effective in children.

Who should not take XTANDI?

XTANDI is not for use in women.

Do not take XTANDI if you are pregnant or may become pregnant. XTANDI can harm your unborn baby.

What should I tell my healthcare provider before taking XTANDI?

Before you take XTANDI, tell your healthcare provider if you:

- have a history of seizures, brain injury, stroke, or brain tumors
- have any other medical conditions
- have a partner who is pregnant or may become pregnant. Men who are sexually active with a pregnant woman must use a condom during and for 3 months after treatment with XTANDI. If your sexual partner may become pregnant, a condom and another form of effective birth control must be used during and for 3 months after treatment. Talk with your healthcare provider if you have questions about birth control. See “**Who should not take XTANDI?**”

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. XTANDI may affect the way other medicines work, and other medicines may affect how XTANDI works.

You should not start or stop any medicine before you talk with the healthcare provider that prescribed XTANDI.

Know the medicines you take. Keep a list of them with you to show your healthcare provider and pharmacist when you get a new medicine.

How should I take XTANDI?

- Take XTANDI exactly as your healthcare provider tells you.
- Take your prescribed dose of XTANDI one time a day, at the same time each day.
- Your healthcare provider may change your dose if needed.
- Do not change or stop taking your prescribed dose of XTANDI without talking with your healthcare provider first.
- XTANDI can be taken with or without food.
- Swallow XTANDI capsules whole. Do not chew, dissolve, or open the capsules.
- If you miss a dose of XTANDI, take your prescribed dose as soon as you remember that day. If you miss your daily dose, take your prescribed dose at your regular time the next day. Do not take more than your prescribed dose of XTANDI in one day.
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What are the possible side effects of XTANDI?

XTANDI may cause serious side effects including:

- **Seizure.** If you take XTANDI you may be at risk of having a seizure. You should avoid activities where a sudden loss of consciousness could cause serious harm to yourself or others. Tell your healthcare provider right away if you have loss of consciousness or seizure. Your healthcare provider will stop XTANDI if you have a seizure during treatment.
- **Posterior Reversible Encephalopathy Syndrome (PRES).** If you take XTANDI you may be at risk of developing a condition involving the brain called PRES. Tell your healthcare provider right away if you have a seizure or quickly worsening symptoms such as headache,

decreased alertness, confusion, reduced eyesight, blurred vision or other visual problems. Your healthcare provider will do a test to check for PRES. Your healthcare provider will stop XTANDI if you develop PRES.

The most common side effects of XTANDI include:

- weakness or feeling more tired than usual
- back pain
- decreased appetite
- constipation
- joint pain
- diarrhea
- hot flashes
- upper respiratory tract infection
- swelling in your hands, arms, legs, or feet
- shortness of breath
- muscle and bone pain
- weight loss
- headache
- high blood pressure
- dizziness
- a feeling that you or things around you are moving or spinning (vertigo)

XTANDI may cause infections, falls and injuries from falls. Tell your healthcare provider if you have signs or symptoms of an infection or if you fall.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of XTANDI. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store XTANDI?

- Store XTANDI between 68°F to 77°F (20°C to 25°C).
- Keep XTANDI capsules dry and in a tightly closed container.

Keep XTANDI and all medicines out of the reach of children.

General information about XTANDI.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use XTANDI for a condition for which it was not prescribed. Do not give XTANDI to other people, even if they have the same symptoms that you have. It may harm them.

This Patient Information leaflet summarizes the most important information about XTANDI. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about XTANDI that is written for health professionals.

For more information go to www.Xtandi.com or call 1-800-727-7003.

What are the ingredients in XTANDI?

Active ingredient: enzalutamide

Inactive ingredients: caprylocaproyl polyoxylglycerides, butylated hydroxyanisole, butylated hydroxytoluene, gelatin, sorbitol sorbitan solution, glycerin, purified water, titanium dioxide, black iron oxide

Marketed by:

Astellas Pharma US, Inc., Northbrook, IL 60062
Medivation Inc., San Francisco, CA 94105
151074-XTA-BRFS

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076-1977-PM

This Patient Information has been approved by the U.S. Food and Drug Administration.

Revised: October 2016

Need another excuse not to shave?

We've got your back.

Join men around the country this fall to Grow & Give. Whether it's a little peach fuzz or a full-fledged beard, you can make a difference for prostate cancer patients.

Sign up your stache:

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ZERO - The End of Prostate Cancer.



ZERO
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MAP YOUR PATH FORWARD WITH ADVANCED PROSTATE CANCER

MyProstateCancerRoadmap.com is an online resource that can help patients and caregivers navigate through advanced prostate cancer topics such as:



UNDERSTANDING YOUR ROAD

You already know about prostate cancer. What is advanced prostate cancer?



CHOOSING YOUR ROAD

Explore your treatment options so you can partner with your doctor to decide what is best for you.



FINDING YOUR WAY

Learn how to adapt to changing relationships and begin to navigate other changes in your life.



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Coming Up!

*December:
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