Prostatepedia[1]

[1]expert insight + advice

Salvage Therapy

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In this issue....

In December, we're talking about prostate cancer that comes back after radiation or surgery.

Treating recurrent prostate cancer is a major focus in my clinic, the American Institute for Diseases of the Prostate (AIDP). I started seeing patients with recurrent disease in 1994 at the University of Virginia and have seen about 1,000 men at AIDP since we opened in 2003. About half of my patients at AIDP have or had recurrent cancer. The others had metastatic disease at diagnosis, or are on active surveillance. In 1999, I myself was diagnosed with metastatic prostate cancer and today remain concerned about recurrence.

I've struggled with the complex issues men with recurrent prostate cancer face. Recurrent prostate cancer is extremely heterogeneous. I have a handful of patients I started seeing in 1994-96 who still haven't developed diffuse metastatic disease and whose cancers respond to minimal treatment. I also have patients with explosive cancer with doubling times of two to four weeks who rapidly developed diffusely metastatic disease.

For much of this time period, the PSA doubling time was the most valuable tool available to determine a cancer's aggressiveness. PSA doubling times more rapid than three months signaled aggressive disease likely to become metastatic, whereas doubling times slower than nine months were often associated with indolent cancer. This was even more pronounced with doubling times slower than 18 to 24 months. These guidelines are still useful: Dr. Phuoc Tran's trial uses a 15-month doubling time or slower as an eligibility requirement.

While nomograms based on doubling time and other clinical parameters are useful, there are still patients whose cancer proves more or less aggressive than anticipated. Determining aggressiveness has been improved by molecular marker tests done on tissue obtained at biopsy or at surgery. The sophistication and utility of these tests are advancing rapidly. I agree with Dr. Stephen Freedland that Decipher is currently the most promising one.

Patients with a rapid PSA doubling time are at high risk for developing diffuse metastatic disease. They often have cancer cells in their blood stream, a common means for the cancer to spread to bone, liver, or other organs. Guardant360 is a blood test that sequences a cancer cell's DNA. We've used the test on more than 60 patients to tailor treatment.

This month we also discuss advances in imaging. Identifying patterns of metastatic spread is useful. Clearly, patients with recurrent disease limited to the prostate bed, irradiated prostate, and/or pelvic nodes are likely to have a better prognosis than those with extensive nodal spread or liver and bone metastases. But the most interesting finding is the possibility of true oligometastatic disease: patients might be placed in a durable complete remission with surgery or radiation. As several of our investigators note, even the most advanced imaging techniques don't identify micrometastatic prostate cancer. Today, imaging alone is not sufficient to identify patients with true oligometastatic disease.

In my experience, patients most likely to benefit from an oligometastatic treatment approach have a PSA doubling time slower than nine months. Durable remissions are much more likely if metastases are limited to the pelvic nodes or a few bone metastases.

I'm very excited by the pace of research in recurrent disease and the quality of the investigators working in this area.

Charles E. Myers, Jr., MD

Contents:

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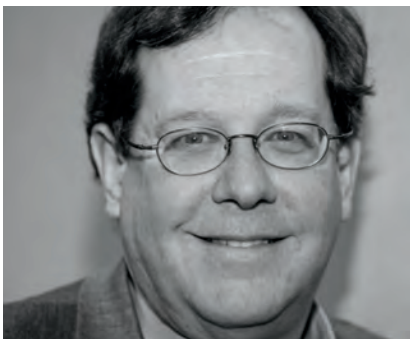
Oliver Sartor, MD
Recurrence After Treatment



Dr. Oliver Sartor, the Laborde Professor of Cancer Research in the Medicine and Urology Departments of the Tulane School of Medicine, is one of the leading researchers in advanced prostate cancer today. He is also the editor-in-chief of *Clinical Genitourinary Cancer* and the author of more than 100 scientific papers.

Prostatepedia spoke with Dr. Sartor about recurrent prostate cancer.

How do we know a man's cancer has started growing again after treatment?

Dr. Sartor: We have two basic algorithms. The first is for radical prostatectomy. A man with no prostate should have no PSA. If you don't have a prostate, your PSA ought to be undetectably low, because there is only one source of PSA—the prostate or prostate cancer. When you have *any* PSA after radical prostatectomy, it is presumptive evidence of prostate tissue.

There are various guidelines for recurrence. If you have a consistent rise in PSA at any level after an initially undetectable PSA, that is considered recurrence. Currently, I'm treating somebody with a 0.05 PSA with radiation therapy, because I believe that he has a recurrence. His PSA was undetectable and then went from 0.01 to 0.02 to 0.03 to 0.04 to 0.05.

"…we start thinking about recurrent cancer when the PSA is detectable after surgery."

It is also possible for men to have a detectable PSA after radical prostatectomy that, on occasion, is not due to cancer. This is called a benign margin and is rarely discussed, but it is present in about 10% of people if you look carefully at the pathology. A benign margin occurs because during surgery the surgeon can cut into the prostate, and particularly down around the apex, but still leave behind a little bit of prostate tissue. If that happens and there are benign prostate retentions post-surgery, you definitely will have a very low PSA that just sits there—doesn't grow, doesn't move.

Extremely rarely, you can have fluctuations so that the PSA goes up and down for reasons we don't understand. I have had that happen to people in my practice.

But the bottom line is that we start thinking about recurrent cancer when the PSA is detectable after surgery because there has to be an explanation. You don't just have PSA after surgery without an explanation. Every PSA needs to be explained.

Patients who recur after radiation are different from those who recur after surgery because you've got a relatively simple, straightforward salvage radiation procedure that can cure a significant number of people post-surgery, but post-radiation you do not have anything comparable. You could do a salvage prostatectomy, but doing prostatectomies in radiated fields results in extremely high rates of incontinence and relatively poor cure rates.

Is that because of the scarring that happens after radiation?

Dr. Sartor: The complications from salvage surgery are due to the scarring after radiation and the poor healing after radiation, but the poor cure rates are because they only treat the prostate. They don't treat around the prostate at all. Surgeons take out prostates; they don't take out a lot of the tissue around them.

The management of the patient with recurrence after radiation

is controversial. You also need to ask why the patient did not get surgery in the first place. Many of these patients could have had surgery but chose not to. You sometimes have a different population. If you've got a post-radiation recurrence, then things get a lot more complex.

In the radiation therapy literature, there have been a variety of ways to define PSA recurrence. The one that is probably the most accepted is the so-called *Phoenix definition*. It is called the Phoenix definition because there was a conference in Phoenix, Arizona, where some prominent radiation oncologists got together and decided that nadir plus 2 represents progression. By nadir, we mean the lowest the PSA goes after radiation treatment. You then just add 2.0 to the PSA. If you go down to 0.4, then nadir plus 2 would be 2.4; if the PSA is more than 2.4, then you have a recurrence.

External beam radiation therapy and brachytherapy—particularly brachytherapy—are also subject on occasion to something called the *PSA bounce*. There is significant literature on the PSA bounce: this is when the PSA goes up and then spontaneously comes back down. It is not well understood, but it is a relatively commonly observed phenomenon. Sometimes after radiation, this bounce can be a little bit problematic.

In general, when people have a PSA recurrence you believe to be cancer, then the appropriate course is to use salvage radiation therapy. Salvage radiation is blind radiation: you radiate the area where the prostate used to be and see what happens.

Surprisingly, that works out quite well. The latest statistics come from a GETUG-AFU 16 study. (GETUG is a French genitourinary oncology

group.) They radiated people with PSAs between 0.2 and 2.0. Once a PSA gets above 2.0, the odds of treating it successfully with salvage radiation begin to go down sharply. GETUG16 used a randomized trial design with over 700 patients. Half of the patients had radiation alone and half had radiation plus hormones. There was no particular imaging—just this blind radiation we typically use.

Five years later, 62% of the men who had blind radiation had no more evidence of PSA progression. That means that 62% of the time in this study, blind salvage radiation worked. That's pretty good. It doesn't mean there may not be relapses later, but most of the time if radiation misses your cancer you're going to progress by less than five years. After five years, 80% of the men who had blind radiation plus hormonal therapy had no more evidence of PSA progression.

Last week, I saw a patient who is an engineer. Smart guy. He just could not believe that blind radiation would fix him because he didn't understand how we knew where his cancer was. (The honest answer is that we don't know where the cancer is; we just radiate.) So he did not get radiation at a time when he was curative because he was convinced that it was going to be unsuccessful.

But the truth is that 62% of men at five years with radiation alone will be cured. In this GETUG16 trial of 8,794 men, which is a prospective, large randomized trial, they showed a survival benefit for men who had radiation in the adjuvant setting. (Adjuvant means there is no PSA present, whereas salvage means there is PSA present.)

There are questions that remain, though. There is a large 1,000-patient trial (RTOG 0534) that had three arms:

one group of men got radiation; a second had radiation plus hormones similar to the GETUG study; and a third had radiation to an area larger than the prostate fossa or bed. They used a larger radiation field than usual in addition to hormones. They did this because nobody knows the optimal size of the radiation field. We just know you need to radiate down around the prostate and that that seems to work a substantial proportion of the time.

What is the role of imaging?

Dr. Sartor: Most patients are incredibly surprised to find out how high their PSA has to be for recurrence to be detected on regular imaging. Some studies say the PSA has to get to about 66.

If you do bone and CAT scans on people with very low PSAs you get more false positives than true positives. In general, it is a waste of time to do bone scans and CAT scans on someone with a PSA of 0.2. The cancer is too small.

The basic understanding of PSA and volume goes like this: if you've got a 40-gram prostate, which is normal, you typically have a PSA around 4. That is called PSA density: how much PSA you make per gram of prostate tissue. It takes 40 grams of tissue to make a PSA of 4.

Nobody knows exactly what that looks like for cancer, but let's imagine for a moment that in order to get a PSA of 4, you have to have a tumor as big as your prostate to make that PSA of 4.

Do you know how many cells are in one gram of tissue? A billion. So when we're seeing a PSA of 0.1, that translates to a gram of tissue and that gram of tissue has a billion cells. The first thing we ought to say is that when you have a PSA of 0.1, you probably already have a billion cells making PSA.

In conventional imaging, we don't detect anything smaller than a centimeter, which is one gram. One cc is equal to one gram. When we do conventional imaging and we say we see anything, what we really ought to say is that you don't have more than a billion cells in one spot.

"Patients who recur after radiation are different from those who recur after surgery."

Of course, if you pick up a handful of sand at the beach and toss it into somebody's yard, that handful of sand literally disappears. You just don't see it. The cancer cells don't spread as single tumors. They typically spread in a disseminating fashion. That is one of the reasons that conventional scanning is so bad for early prostate cancer detection.

We needed something more sensitive. And now we have imaging that is more sensitive.

How much more sensitive is the new scanning?

Dr. Sartor: At least ten times more sensitive. Now, instead of seeing a billion cells, we can probably see 100 million cells in one spot. These newer scans aren't perfect. No scan that we have is perfect.

What are some of the newer scans?

Dr. Sartor: The first scan to come on board and gain approval in the United States is the Choline PET/CT

at the Mayo Clinic. The Choline PET/CT is unequivocally more sensitive than both bone and CAT scans. It's a better test. It is able to find cancers and areas of dominant disease that are potentially treatable.

There is not a lot of data, but Drs. Jeffrey Karnes and Eugene Kwon at the Mayo Clinic use the Choline PET/CT scan to try to cure people with disease in their pelvis. These are post-radical prostatectomy and post-radiation patients with PSAs higher than 2.

Dr. Kwon tells me they scanned about 400 people. They found 52 patients with pelvic-only disease. That means about one in eight patients had pelvic-only disease. They then operated on those 52 patients. About half of those 52 patients seemed to have some sort of sustained response after having had a full lymphadenectomy, typically done by Dr. Karnes. That means about one in 16 can be potentially cured with surgery. The follow-up was not very long, so we don't know yet whether or not they were actually cured.

The Choline PET/CT gives you more sensitivity. There are places other than the Mayo Clinic that offer Choline PET—there is a place in Scottsdale, Arizona, and a few in Europe—but it is a very limited subset.

What about PSMA (prostate-specific membrane antigen)?

Dr. Sartor: There is head-to-head data indicating that PSMA imaging is more sensitive than the Choline PET/CT imaging. In a variety of ways, PSMA imaging is evolving rapidly. There are a series of small molecules that bind. There is one from Johns Hopkins University called DCFPyL that is a second-generation small molecule that gives nice images. There is also a group in Heidelberg, Germany, that has been using a compound called PSMA-617.

There are a variety of small molecules now. These small molecules are tagged with various isotopes. Gallium-68 is one of the favorites. You can do positron emission tomography (PET) with it by putting it on an F-18. There are different isotopes. You can either do SPECT or PET, SPECT being the single-photon emission computed tomography.

There are different ways of approaching this. I'm not sure we have all the right isotopes. I will say that there are places in the United States beginning to do PSMA—Johns Hopkins is now doing it on a protocol. *[See the conversation with Dr. Phuoc Tran on page 28 for more about that trial*]. NIH is going to have a protocol soon, in combination with Johns Hopkins. Cornell is also going to have one. UCLA has one. UCSF is either getting one, has one now, or is at the beginning.

These newer ways of imaging are more sensitive, so, of course, when you're imaging with a more sensitive agent, you're going to find more than what you used to find.

A lot of what you find are individuals with a limited amount of metastases, whether in the pelvis or outside the pelvis. This is called oligometastatic disease. There are different definitions of oligometastatic disease: some say up to three lesions, some say up to five. But there is a limited number.

What is the treatment approach for these limited lesions that better imaging is detecting?

Dr. Sartor: Some have been trying to radiate these lesions, also perhaps using hormones, or perhaps using chemotherapy, hormones, *and* radiation. We don't have a lot of data at present, so I'm not able to give you good statistics on how this is working. It is also important to understand that the cost—emotional, financial, and toxicity—of these efforts carries a burden.

When we give radiation to areas that we see, we positively know that there is going to be more disease in many of these men because we know the limitations of imaging are such that we cannot image every last cell. In that scenario, hormonal therapy might be used.

Some have used these more sensitive imaging techniques to try to radiate the lesions and then see what happens, to see if they can delay the onset of other more toxic therapies such as hormonal therapies and chemotherapy. That does, in fact, seem to work. There is now data to show that if you radiate selective lesions, it seems to delay the time to the use of androgen deprivation.

Everything I've said so far about recurrent cancer really applies to men who have hormone-sensitive disease or castrate-sensitive disease. But there is a conceptual approach where you divide oligometastatic disease into those men who are hormone-sensitive and those that are castrate-resistant. We can then take these same scenarios forward with those who have castrate-resistant oligometastatic disease. Maybe if you radiate those men they can avoid other therapies.

This is more conjectural and is an area of vibrant ongoing discussion.

Here's a case of mine that illustrates the issues nicely. The patient went to the Mayo Clinic and had a totally negative Choline PET/CT after spine radiation. He was previously

classified as oligometastatic at Mayo before the spine radiation.

We were hoping to go find maybe one or two more lesions to radiate, but instead when he went to Johns Hopkins for a PSMA scan they found so many lesions we couldn't count them all. This gets to a basic point: how do you define oligometastatic disease and what do you want to do with that information?

There is a gentleman I see in New Orleans who went to the Mayo Clinic where they found that he had oligometastatic disease in his chest. Now, that is not always easy to radiate because you will hit the lungs and other organs. He has asked me, "How long will it be before I get into trouble from these mets in my chest?" I said, "We don't know exactly. It could be a couple of months or it could be a couple of years." He said, "Why don't we just watch it and see what happens?" This guy, after he knew that it had spread and that I was unable to define when he would have symptoms, wanted to wait to see what happened. That is perfectly acceptable.

I have patients who get chemotherapy, hormonal therapy, and radiation therapy in an attempt to eradicate their oligometastatic disease. I have other people who say, "Doc, I'll take a rain check on this and see you in three months to see how I'm doing. How does that sound?"

I can't disagree with either approach because we don't necessarily know how fast the cancer is going to grow. You could have just a few lesions for years.

The symptoms caused by metastases also vary tremendously according to location. You can have relatively large retroperitoneal lymph nodes that cause no symptoms whatsoever. The location matters and the growth rate matters.

Not everybody wants to be cured of their cancer; some people just want to live with their cancer in a symbiotic state and not have the cancer screw up their lives.

Some patients are very aggressive; they're seeking answers. There is another group of patients who are perfectly happy to avoid treatments as long as the cancer doesn't cause them any symptoms. It's just as important to respect their desires as

"What the patient thinks is right."

it is to figure out how to help people who want to be cured and are willing to pay a high cost in an attempt to get cured, even knowing that we don't have data to indicate cure is even achievable.

By high cost do you mean financial or toxicity?

Dr. Sartor: Typically, when I talk about cost, I'm referring directly to toxicity cost. I have a patient who had an oligometastasis detected by conventional scanning—he didn't have any fancy scans. I put him on hormones for four months and then radiated the lesion. He hated the hormones. They drove him crazy. He got hot flashes. He became depressed. I had to send him to counseling. He felt horrible.

Three or four years later, he has a completely undetectable PSA and his testosterone is fully recovered. By treating his oligomets with the combination of hormones and radiation, I'm giving him a pretty prolonged period of time during which he can keep his hormones levels normal and not deal with those issues again.

These newer imaging techniques are great for finding more disease, but what do we do when we find it? How that translates into better patient care is an evolving paradigm and highly individualistic. It's dependent not only on the location and growth rate of the lesions, but also on what the patient involved wants. It isn't cut and dry. It isn't simple, but rather complex.

I explain to people before scanning that you don't know what you're going to find. You don't know where you're going to find it. You don't know how many mets we're going to find. After you find whatever you're going to find, we have to tailor a treatment plan to what is right for that patient, but only in the context of his permission and his desires. To me, that is the art of being a good physician.

Do you think doctors should discuss with patients before scanning what they will do if they do find more cancer?

Dr. Sartor: Absolutely. If somebody tells me that they don't really care what we find, then why should I go scan them?

I do believe that with more information we can make better clinical decisions. In the end, that is really what I treasure. I want to be able to make the best clinical decision for my patient, and if I know where the cancer is, I can potentially add value to the decision-making. That doesn't mean it adds value every time and that doesn't necessarily mean that what I think is right. What the patient thinks is right. Pp[1]

James Eastham, MD
Surgery After Radiation Therapy

Dr. James Eastham, Chief of Memorial Sloan Kettering's Urology Service, is a surgeon who specializes in nerve-sparing radical prostatectomy and salvage radical prostatectomy after radiation therapy.

Prostatepedia spoke with him recently about surgery after radiation therapy for prostate cancer.

How did you come to focus on prostate cancer?

Dr. James Eastham: I became interested in prostate cancer primarily because it is a very intriguing disease. In some cases it is absolutely lethal, but in many others it has a benign course. Many patients will die *with* prostate cancer rather than *of* it. The intellectual challenges of sorting out who needs treatment and who doesn't were appealing to me.

The second side of it is that radical prostatectomy is a very complex operation in terms of balancing cancer-control goals with quality-of-life goals. It varies from patient to patient. While I only treat men with prostate cancer, it's not as if I do the same thing every day, because the surgery varies depending on the risk posed by the cancer. That is how I got interested in the disease: the challenges that it poses.

How do you know when a man's cancer has started growing again?

Dr. Eastham: It depends on how the patient was initially treated. If a man has been treated surgically, the expectation is that his PSA test goes to what is called nondetectable, which is the lower limit of whatever PSA assay or test he is being checked with, and that it stays nondetectable.

> *"…patients with biochemical recurrence have no signs of disease on any imaging studies.."*

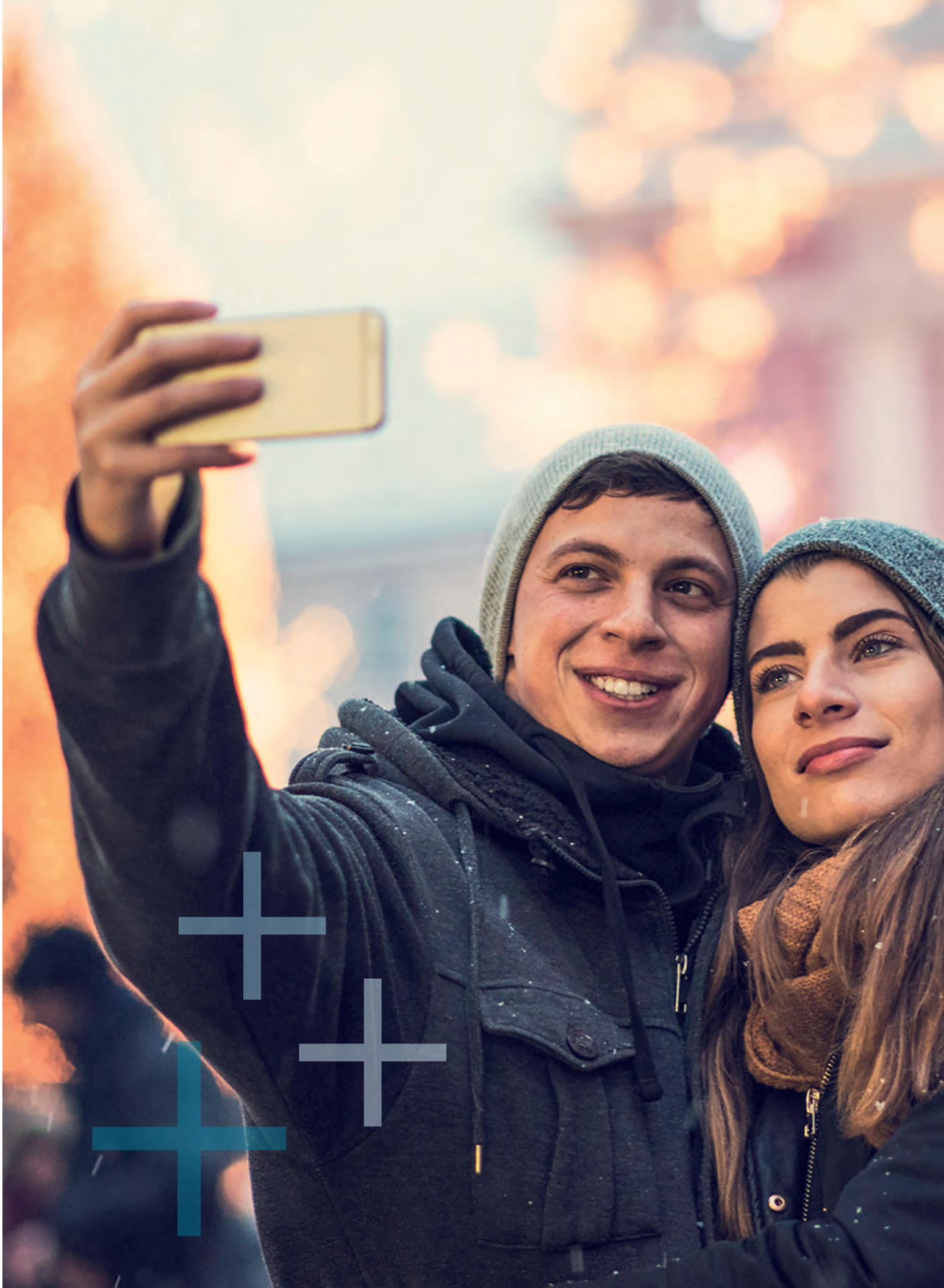
If, after surgery, his PSA becomes detectable and, after checking it again a few weeks later it's *still* detectable, that signals a recurrence. With surgery, identifying a recurrence is easy because the PSA is either zero or it isn't: nondetectable or detectable.

Detecting recurrence after radiation therapy is a little bit more complicated because radiation doesn't completely eliminate the prostate. After radiation therapy, the PSA is expected to drop to very low levels. PSA is still produced because some of the benign prostate tissue remains. Following radiation, the expectation is that the PSA stays at a low level and does not trend upward. The PSA may go up a little bit and it may go down a little bit, but overall there should not be much of an increase over time. Thus, there is some interpretation in terms of what the PSA values mean after radiation therapy.

What we don't want to see after therapy is a PSA that is trending upward. A rise in PSA after therapy, regardless of what that therapy happens to be, typically signifies that something is going on. We then try to determine what that something is and whether the recurrence is high or low risk using individual clinical information.

Is that rise in PSA what we call biochemical recurrence?

Dr. Eastham: Yes, a rising PSA after treatment is called biochemical recurrence. Biochemical recurrence after surgery means a patient has a confirmed detectable PSA. Biochemical recurrence after radiation therapy has a very specific definition, which is the lowest PSA that the man achieved plus 2 points of PSA. These are the definitions of biochemical failure.



Typically, patients with biochemical recurrence have no signs of disease on any imaging studies. They only have PSA failure. We know something is going on, but we don't know where, how, and how much; PSA is far more sensitive than any of the imaging tools that we have.

What is local recurrence?

Dr. Eastham: Local recurrence means that, to the best of our ability to determine, we believe the cancer is only in the area of the prostatic fossa or bed and has not spread beyond that. This means that after surgery, we believe the cancer cells making the detected PSA are only in the area where the prostate used to be, so in the *local* area where the prostate was prior to surgery. After radiation therapy, it means that we believe the cancer is just in the prostate itself.

Typically, if a patient experiences biochemical recurrence, imaging studies are performed to evaluate for disease outside the prostate. Those imaging studies, of course, would have to be negative for the patient to be considered to have local recurrence. After that, if the patient had initially been treated with radiation, we would do a biopsy of the prostate to check for the presence of cancer.

The story is a little different following surgery than it is following radiation therapy, but in both cases, we believe the disease is only in the area where the prostate was after surgery or is after radiation therapy.

What are some of the imaging tools that you use—conventional and newer techniques?

Dr. Eastham: The conventional tools are a bone scan and a CT scan of the abdomen and pelvis. The bone scan, of course, checks for bone metastases. The CT scan primarily looks at soft tissue, meaning lymph nodes and other organs in the body, to see if there are any radiographic or imaging signs of recurrent disease. One can also use an MRI scan to look at the prostate area. The MRI can be used to detect local recurrence after either surgery or radiation therapy.

"Surgery after radiation therapy is used less frequently for a variety of reasons."

There are some other types of imaging studies, in particular PET imaging scans, which are currently reported as being more sensitive imaging tools to detect areas of recurrence.

What is the typical treatment pathway for a man who has recurrence after radiation therapy?

Dr. Eastham: If a man has local recurrence after radiation therapy, we do an assessment of his cancer risk as well as some other features, like his age and health. If he has a relatively short life expectancy, we would manage him differently from someone who has a very long life expectancy.

"One specific treatment isn't right for all patients."

There are several different strategies to eliminate prostatic tissue. They all have their pros and cons. Sometimes we use just observation, meaning we believe the cancer will grow slower than other aspects of the patient's health and won't cause problems. One can also use hormonal therapy.

Is surgery after radiation therapy a controversial approach?

Dr. Eastham: It's about using the right treatment in the right person. Surgery after radiation, called salvage radical prostatectomy, is not for everyone. Certainly, many men initially treated with radiation therapy chose radiation because they didn't like some aspect of surgery. Some men, even though they have recurrence after radiation therapy, *still* don't want an operation. And that is reasonable: we are all individuals and have choices.

Surgery after radiation therapy is used less frequently for a variety of reasons. It's a very technically demanding operation. It is very different from prostate surgery in a man who has not received radiation therapy.

First, there is a significant amount of scar tissue after radiation therapy. Normal anatomy is completely distorted. Many surgeons opt not to do the procedure because it is very different and very difficult, which is a reasonable choice. One should only be doing what one is comfortable doing.

Second, surgery after radiation therapy is associated with a variety of risks. Most importantly from a quality-of-life standpoint, the risks of incontinence and erectile dysfunction are much higher in a patient who has undergone prior radiation therapy than in a man who has not received prior radiation. We have to discuss

quality-of-life issues in some detail with a patient rather than just immediately recommending surgery in the case of radiation failure.

There are other salvage treatment options as well. Some have not been used for very long, but are now in more frequent use. Some patients receive salvage radiation therapy. One can use cryotherapy, which freezes the prostate. One can use other ablation strategies, like heat or electricity, to destroy tissue.

Ablation strategies and salvage radiation are far less invasive than surgery. At least in the short term, they are associated with fewer risks and better quality of life than salvage radical prostatectomy. Many of the studies suggest, though, that long-term cancer control outcomes of these strategies are either unknown or not quite as good as with surgery itself. Again, we balance quantity versus quality of life.

Aren't erectile dysfunction rates pretty high already after surgery?

Dr. Eastham: Not necessarily. It depends on a variety of different things: the man's baseline function; his cancer; his age; and, to some extent, who did the operation. Many men will recover erectile function after radical prostatectomy, but if they undergo any kind of salvage treatment, erectile function rates go down.

What about open versus robotic surgery in a salvage setting?

Dr. Eastham: The bottom line is that whatever the surgeon is most comfortable doing will offer the patient the best outcome. We know that robotic surgery is a less invasive procedure than open surgery, so typically there is less pain, shorter hospital stays and, importantly, less blood loss. All of these facilitate a little bit easier recovery.

In the salvage setting, meaning robotic surgery after radiation therapy, the other benefit that has been shown with robotic versus open surgery is that there is a lower risk of the development of scar tissue in the area where we sew the bladder and urinary tube, the urethra, back together. This area is called the bladder neck. Scar tissue along the bladder neck, called a bladder neck contracture, happens far less frequently following robotic surgery than following open surgery. This is a benefit. The patient will require fewer procedures to manage that scar tissue.

"...robotic surgery is a less invasive procedure than open surgery."

Do you use hormone therapy in conjunction with these salvage therapies?

Dr. Eastham: It's not routine. Some of the ablative strategies—salvage cryotherapy, salvage radiation therapy—will use hormonal therapy in conjunction, but hormonal therapy alone may actually be appropriate for some men. This is not a curative approach, but if a man is of an age and health that his life expectancy isn't very long, then watching him with selective hormone therapy alone is certainly reasonable.

For men with only a local recurrence and a longer life expectancy, we typically look for a more definitive treatment strategy to try to eliminate the cancer. Hormonal therapy isn't without side effects. Again, it's all a balance of a variety of different factors.

What does hormonal therapy do to erectile dysfunction rates in men who have had salvage therapy?

Dr. Eastham: It's essentially 100%.

Because there is no testosterone during hormonal therapy?

Dr. Eastham: Correct. Hormonal therapy typically results in erectile dysfunction, hot flashes, potentially difficulties with concentration, weight gain, and loss of lean muscle mass. Longer term, there is a risk of osteoporosis. There's also the risk of metabolic syndrome, which impacts glucose or sugar, cholesterol, and heart disease risk. There are a variety of things that come into consideration with hormonal therapy. It certainly isn't like taking a multivitamin. Hormonal therapy is a treatment, a cancer treatment, which has consequences.

Do you have any advice for patients who have been told they have biochemical or local recurrence?

Dr. Eastham: I think patients need to explore their treatment options. One specific treatment isn't right for all patients. There are a variety of options. We as physicians don't know the exact best option in every single case. We have to investigate what the patient's concerns are and weigh them with their cancer control issues. Two individuals may have a very similar clinical picture, but once they've discussed the treatment options with their doctors, they may make very different decisions about how to move forward. It's important to know all of your treatment options and not just make a knee-jerk selection. Pp[1]

Neha Vapiwala, MD
Radiation Therapy After Surgery

Dr. Neha Vapiwala, an Associate Professor and the Vice Chair of Education in the Department of Radiation Oncology at the University of Pennsylvania, focuses on biological and technological improvements in the delivery of photon- and proton-based radiation.

Prostatepedia spoke with her recently about radiation therapy after surgery.

How did you come to focus on prostate cancer?

Dr. Neha Vapiwala: When I finished my residency training, I was offered the opportunity to join the faculty at the University of Pennsylvania as a Residency Program Director and genitourinary radiation oncologist. Within the first year of building my own clinical service and caring for my patients and their families, I knew that prostate cancer patients were my calling. So I guess it was a combination of good timing, opportunity, and passion for treating this group of patients.

In which situations is radiation therapy after radical prostatectomy used?

Dr. Vapiwala: There are two main categories that apply when we think about post-prostatectomy radiation. The first category is adjuvant. Adjuvant radiation by definition means that there is no clear evidence that the cancer is there or has come back at the time of radiation, but the patient is at high risk for disease recurrence after surgery if no additional therapy is given. This risk is determined based on the individual's pathology findings at the time of surgery, and increasingly on genomic test findings—factors that leave us concerned enough about the risk of the cancer coming back that we use adjuvant radiation therapy with the goal of recurrence prevention.

"I tell patients it's like having a variety of tools."

I often tell patients, "If you signed up for a marathon, would you risk stopping short of the finish line or would you try to do whatever was in your power to try and cross it?" That is the idea of adjuvant radiation. You don't have any evidence of disease at the moment, but you do have the presence of certain features associated with an increased chance of the cancer coming back. Offering radiation is an attempt to try to get you to a lower risk of the cancer coming back. The recurrence risk is never going to be zero no matter what you do because there is no 100% cure that works 100% of the time. With favorable-risk prostate cancer, you may have a 10 to 15% lifetime chance of the cancer coming back after surgery alone. But if you have positive margins, cancer outside of the prostate invading the seminal vesicles, and/or worrisome genomic test scores, that lifetime risk may be doubled or tripled. So we use adjuvant radiation to try and knock you back down to that 10 to 15% lifetime risk.

The other category of postoperative radiation is—rather unfortunately—called "salvage radiation." Unlike adjuvant cases, this is when you already have a rising PSA level, or it never went down or reached zero after surgery. Normally, after surgery, your PSA should drop to zero and stay there. Salvage radiation patients are those in whom the PSA has already started to rise. There is established reason to treat. The disease has declared itself (or the patient has declared himself) as having cancer recurrence. So we use radiation to try to get rid of the cancer that has come back in the hope that it is located in the area where the

prostate used to be, what we call the prostatic fossa or prostate bed.

The problem is that there is a continuous risk of the cancer spreading beyond this local area, depending on when and at what PSA level you treat. The longer the patient has waited with a rising PSA to get salvage radiation, the higher the absolute PSA level is likely to be when that salvage radiation is delivered. Absolute PSA level, PSA velocity (i.e. the pace at which it has been rising), elapsed time since surgery, and the original pathology findings can all predict for a higher chance that salvage radiation alone is not going to work. As you can imagine, if you give the cancer enough time and/or if it is aggressive enough, you lose a window of opportunity where it could still be sitting in the prostate bed and risk giving it time to spread. And then salvage radiation to the prostate bed for a "second shot" at cure is unlikely to be sufficient at that point.

What is the role of imaging in this situation?

Dr. Vapiwala: Patients ask me all the time, "How do you know where the cancer is?" I say to them, "I don't know." I go by the natural history of prostate cancer which we learned from the unfortunate stories of men who had prostate surgery, developed a rising PSA but, for whatever reason, did not obtain treatment and just let the PSA keep rising (what we call "patterns of failure"). Eventually, the cancer shows up on an imaging scan. From this natural history, we have learned that in many patients the cancer tends to show up in the local neighborhood, most often at the site of the surgical anastomosis. But in some patients, the cancer appears at distant sites in the body, with or without and disease in the prostate bed. At that point, the man has gone

from being potentially curable with salvage radiation to not being curable. The challenge, of course, is knowing who is in which category.

With the conventional imaging tests we presently have, we are unable to detect down to the level of individual cancer cells and thus unable to adequately distinguish those who can benefit from salvage radiation alone versus those who need systemic therapy (i.e. hormone therapy or chemotherapy) in addition to or instead of salvage radiation.

If I had better imaging tests, and there are certainly some agents and special radiotracers in development as we speak that are more sensitive and may be able to detect far smaller tumor deposits than was ever possible before, I might be able to better distinguish those patients for whom the cat is already out of the bag versus those I still have a chance to help with local therapy. I say to patients all the time that the catch-22 is that if we wait for your PSA to be high enough so that we can see the cancer on a scan, we might have waited too long. You want to treat patients early, but in doing so you may overtreat—in the case of adjuvant—or you may treat an incomplete target since you can't see the cancer.

What kind of radiation therapy is used in a salvage setting?

Dr. Vapiwala: It is usually photon therapy. There are different techniques for delivering photon therapy. There is 3D-conformal, which is the old-fashioned way, relatively speaking. We don't typically use that as much anymore. There is intensity-modulated radiotherapy, or IMRT. There is also a variation of IMRT that is called volumetric-modulated arc therapy, or VMAT. In arc therapy, the linear accelerator radiation delivery moves

around the body, rather than using single-static beams in fixed positions.

These are all different ways to deliver ionizing radiotherapy. I tell patients it's like having a variety of tools. I have a task in front of me with a goal of optimizing the task for the sake of the patient, and I have a set of ratchets. I don't know which one I need to get the job done, but I know at the end of the day what I need to achieve. I'll use whichever tools I have available to me to achieve the goal of getting maximum radiation dose to the prostate bed—the area we consider most likely for cancer cells to come back—and minimal dose to the surrounding structures. This is the general approach we take.

Do you combine radiation therapy with hormonal therapy?

Dr. Vapiwala: That is an evolving story. For the longest time, we didn't have data to support combining hormonal therapy with radiation therapy in the postoperative setting. We certainly did have evidence to support use in patients who still have their prostate, but we extrapolated and applied it to that group in the postoperative setting.

The truth is that we now have data, at least in abstract form from RTOG 9601, that supports giving radiotherapy and androgen deprivation therapy in patients with rising PSAs. So, again, this is the salvage and not adjuvant group. The problem is that in that trial (RTOG 9601), they gave patients two years of an oral pill that is often difficult to tolerate and is not the typical preferred form of androgen deprivation therapy. (Normally, we use the injectable drugs like GnRH agonists such as Lupron.)

This antiandrogen pill can cause breast enlargement, or gynecomastia, and liver abnormalities. RTOG 9601 also showed that a subset of patients —those with higher PSAs at the time of salvage radiation—benefit from adding hormonal therapy to radiation. This makes sense, as the higher the PSA before you start salvage radiotherapy, the greater the chances are that the cancer is no longer sitting where the prostate used to be located. If you were to add a systemic therapy, you would expect that to be the group that would benefit.

But, like I said, this is an evolving story. We'll have more studies that will further refine when to use hormonal therapy in a salvage setting, what to use, and for how long. For the time being, it is often at the discretion of the treating physician.

What are the side effects of salvage radiation? Are the side effects worse after salvage than primary radiation therapy?

Dr. Vapiwala: That is always a concern. I say to all my patients that any treatment is typically tougher on the second round, in that the body has had one hit already, and in this case, the anatomy has been altered. There may be lingering side effects from the initial treatment, whether it is surgery or radiation. If a patient is continent, potent, has had some time to heal after surgery, and does not have any clear postoperative complications, he is going to have the best chance of doing quite well with salvage radiotherapy. The tolerability for a patient like that is very high compared to a patient who is still having stress incontinence and erectile dysfunction.

There are patients who go through radiotherapy and don't necessarily get worse, but may never get better. This really depends strongly on that preradiation therapy baseline—how they're doing before salvage radiation. If the patient is younger, that helps. If the patient doesn't smoke or is not diabetic, that helps as well. That is all part of the story.

Is there anything else you think patients should know about salvage radiation?

Dr. Vapiwala: We now have an update of the Stephenson nomogram, which has traditionally been used as a tool for physicians to weigh the odds that a man's disease is still local vs. distant, and whether or not a local treatment like radiation would help. I look at every patient with a rising PSA after surgery in that context, even those that are getting adjuvant radiation. What are the odds that this man's disease is local? That I'm going to be helpful to him?

The updated nomogram, which came out in August 2016, is critical because it takes into account ultrasensitive PSA levels. We are now in the realm of rampant ultrasensitive PSA testing so that we get really low values well below the historical definition cut-points of recurrent disease. It used to be we didn't see PSAs less than 0.2. (The lab didn't measure anything less than 0.2.)

This nomogram took almost 3,000 patients treated with postoperative radiotherapy and demonstrated quite nicely that the lower the PSA level is at the start of salvage radiotherapy, the more likely there would be a benefit to the patient with salvage radiation. The data suggest that you should not watch the PSA levels rise; even with these ultrasensitive values under 0.2, there appears to be a benefit not just for PSA control, but for avoidance of distant metastasis development.

That is something I want patients to know because I think many surgeons are accustomed to telling patients to wait until the PSA is higher. These new data would suggest that there is no floor. You want to act earlier. Pp[1]

Francesco Montorsi, MD

Salvage Lymph Node Dissection

Dr. Francesco Montorsi is Director of the Urology Unit and Chief Scientific Officer of Scientific Institute Hospital San Raffaele in Milan, Italy. He is also Professor in Urology and Director of the Residency Program in Urology at the University Vita-Salute San Raffaele in Milan. Montorsi specializes in the pathophysiology, diagnosis, and treatment of prostate cancer, urologic oncology, benign prostatic hyperplasia, and sexual dysfunction. He has written or coauthored more than 1,000 articles and book chapters and is the Editor Emeritus of *European Urology* and the Adjunct Secretary General of the European Association of Urology.

Prostatepedia spoke with him recently about salvage lymph node dissection.

How many patients recur after radical prostatectomy?

Dr. Francesco Montorsi: Up to 30% of prostate cancer patients experience biochemical recurrence at long-term follow-up, which is defined as two consecutive PSA rises ≥0.2 ng/ml after a radical prostatectomy. When we talk about local recurrence, we are talking about recurrence located in the prostatic bed, where the prostate was before surgery. On the other hand, metastatic disease is the recurrence in systemic sites. There is also a recurrence in the lymph nodes, which is one of the most common sites of recurrence in patients who receive treatment with curative intent. Of note, the risk of recurrence significantly varies according to individual patient characteristics, where men with more aggressive disease are at increased risk of experiencing disease relapse after surgery.

How do patients with metastasis in their lymph nodes do compared to patients who have metastasis in their bone or organs?

Dr. Montorsi: We have done some studies at San Raffaele Hospital on this subject. We have also done studies on large databases coming from the United States. There are two different scenarios. In the first scenario, a patient has metastasis of prostate cancer at diagnosis. We know that patients who have lymph node metastases have a better prognosis compared to men who have metastases in their lungs or visceral metastases at presentation. Moreover, patients with bone metastases have an intermediate prognosis between the two groups.

When considering patients experiencing recurrence after primary treatment, in a study we published in *European Urology* a year ago, we were able to determine the patterns of recurrence in men treated with radical prostatectomy who had lymph node invasion at the time of surgery. We showed that up to 30% of those patients had local recurrence or recurrence in the pelvic lymph nodes. Moreover 13% had recurrence in the pelvic lymph nodes and 40% had skeletal recurrence. Only 10% of them had a visceral recurrence—recurrence in their internal organs.

Patients who had a recurrence located in the pelvic and retroperitoneal lymph nodes had a better prognosis compared to those with visceral or skeletal metastases. These patients might be affected by a different kind of disease, which can be nonsystemic. In selected patients, we can still think about surgery to reduce the use of systemic therapies in the future.

What is the role of newer imaging techniques?

Dr. Montorsi: Novel imaging modalities, such as Choline or PSMA PET/CT scans, will play a major role in the assessment of prostate cancer patients who experience recurrence after primary treatment. At our hospital, Choline PET/CT is available and all patients with rising PSA after surgery with a clinical suspect of lymph node or distant recurrence

are submitted to this imaging. However, the performance characteristics of Choline PET/CT are suboptimal at very low PSA levels.

On the other hand, PSMA is a new very promising tracer and can substantially improve our ability to detect metastases even in patients with very low PSA levels after surgery. For example, approximately 50% of patients with a PSA below 1 after radical prostatectomy have a positive PSMA PET/CT scan. This is not the case for other imaging studies such as the Choline PET/CT or standard imaging modalities bone scan, or CT scans.

Is it just a matter of time before PSMA is available more widely?

Dr. Montorsi: Not only a matter of time, but also of cost. In Europe, this technology will be diffused over the next few years. We already observed a widespread diffusion of Choline PET/CT and we expect the same of PSMA. I know that in the United States, it's a little bit different: not all centers are able to provide the Choline PET/CT. I think that in the future, these newer imaging modalities will substantially impact our management of prostate cancer patients, particularly in the recurrent setting.

What is lymph node dissection?

Dr. Montorsi: When we talk about lymph node dissection, we mean removing all the lymph nodes, which are the landing sites for prostate cells. In prostate cancer, we should remember that the primary sites of lymph node involvement are the pelvic nodes, which are the external iliac, obturator, and internal iliac lymph nodes. We normally extend our pelvic extended dissection to the crossing between the ureter and the common iliac vessels. This is the standard extended template for a lymph node dissection performed at our center. We select which of our patients will receive a lymph node dissection along with a radical prostatectomy based on their disease characteristics presentation.

"Up to 30% of prostate cancer patients experience biochemical recurrence."

"Patients who had a recurrence located in the pelvic and retroperitoneal lymph nodes had a better prognosis compared to those with visceral or skeletal metastases."

According to European Association of Urology guidelines, patients with a higher PSA, higher clinical stage, and higher Gleason score should be considered for a lymph node dissection. We use a predictive tool that gives a probability of lymph node invasion. When this score is higher than 5%, all of these patients receive a lymph node dissection. This applies for lymph node dissections performed at the time of radical prostatectomy. When we talk about lymph node dissection in recurrence, the template is a little bit different because we have to clear all of the nodal stations located in the retroperitoneum. It's a different template and a different anatomical concept of lymph node dissection. We know in the recurrence setting that we need to do an extended template in the retroperitoneum to be able to completely detect the extent of lymph node involvement.

What are the differences between robotic versus traditional surgery for lymph node dissection?

Dr. Montorsi: The template performed with the two techniques is the same. However, the main advantages associated with robotic surgery are related to better perioperative outcomes, shorter length of stay, and reduced blood loss. Moreover, according to recent studies the robotic technique might improve our ability to remove lymph nodes in sites difficult to reach with open surgery. We now use robotic surgery for salvage lymph node dissection because we consider robotic surgery the approach of choice for every case performed at our institution. We think we are able to get good anatomical exposure and are able to remove all the lymph nodes, while reducing the risk of complications and the morbidity of the surgery. We recently published a study in September 2016 in *European Urology*, describing our technique. It's feasible.

However, we are still in the learning curve period. In particular, we had a couple of injuries in the big vessels, but we were able to manage and repair those robotically. We had good outcomes during the postoperative period in terms of complications. Eventually, we were able to remove sufficient lymph nodes to provide extensive dissection in these patients. The robot will play a role, but the surgeon needs to have sufficient experience to perform this surgery safely.

So then there's a learning curve for how to safely perform robotic lymph node dissection. As more and more surgeons become trained in robotic lymph node dissection, will that learning curve shorten?

Dr. Montorsi: That is what we hope for. We now have excellent training programs for robotic surgery. We have simulators, dry labs, wet labs, and

> *"We now use robotic surgery for salvage lymph node dissection."*

modular training. This kind of surgery will be performed safely and efficiently in a lot of centers in the future.

What about complications after lymph node dissection in the salvage setting?

Dr. Montorsi: Complications after lymph node dissection in the salvage setting are common, because patients have already had a radical prostatectomy and most of them received adjuvant or salvage radiotherapy. All these previous treatments negatively impact the risk of complications.

> *"The robot will play a role, but the surgeon needs to have sufficient experience."*

Individuals who have had previous radiotherapy have different tissues. There is a scarring process after radiation that impairs our ability to do lymph node dissection in a salvage setting

without complications. Common complications may be related to injuries to the nerves, the ureters, and the big vessels. We can also have problems after surgery related to a delay in the recovery of the bowel function.

What about erectile dysfunction? Is that higher after lymph node dissection in a salvage setting?

Dr. Montorsi: No, it's not so common. These patients have usually already received a radical prostatectomy, which impairs their erectile function. Often, they are on ongoing androgen deprivation therapy that also impairs erectile function. With a lymph node dissection in a recurrence setting, we're not really doing any *further* damage to their erectile function.

Do you give hormonal therapy and radiation at the same time that you do a salvage lymph node dissection?

Dr. Montorsi: It depends on the physician preferences and on individual patient characteristics. We know that selected patients might benefit from adjuvant radiotherapy and systemic therapies after surgery. However, salvage lymph node dissection was developed only recently. A lot of centers are currently doing it, but still we don't know the best timing for hormonal therapy. The ideal setting for lymph node removal is in patients who have not received hormonal therapy. We can assist to a degree with postoperative PSA levels so that we can then postpone or avoid hormonal and other assisting therapies. However, this is not always the case. We are unlikely to cure patients with extensive disease in their lymph nodes at the time of surgery with just lymph node dissection. These particular individuals might indeed benefit from adjuvant treatments like hormonal therapy in a multimodal setting. Pp[1]

Stephen Freedland, MD: Recurrence After Salvage Therapy

Dr. Stephen Freedland, Director of the Center for Integrated Research in Cancer and Lifestyle, Co-director of the Cancer Genetics and Prevention Program and Associate Director for Faculty Development at the Samuel Oschin Comprehensive Cancer Institute, is a urologist at Cedars-Sinai in Los Angeles, California. His approach involves treating the whole patient and not just a man's prostate cancer.

Prostatepedia spoke with him recently about using the genomic test Decipher to predict whether or not a man's cancer will come back after salvage therapy. In the interest of full disclosure, Dr. Freedland has done research with both Myriad Genetics, the maker of Prolaris, and GenomeDx, the maker of Decipher.

How did you come to focus on prostate cancer?

Dr. Stephen Freedland: I was very interested in cancer growing up. I had some family experiences that led me to want to take care of cancer patients and ultimately make a difference. I decided early on in medical school that I wanted to be a surgeon because, in my mind, that was the best way to treat cancer: pick it up early and cut it out. Twenty or so years ago that was the mindset. We've certainly progressed a long way. It then really became a question of what type of cancer would I focus on. For multiple reasons, prostate cancer and urology seemed like a very good fit for me.

How common is it for a man's prostate cancer to begin growing again after he has had salvage radiation therapy?

Dr. Freedland: Salvage radiation implies they've had some sort of primary treatment, often surgery, and that that has failed, and now they are having a second line of, hopefully, curative treatment.

With each successive line of treatment, the success rates go down. About a third of the men, on average, will fail after surgery. As we're operating on more and more high-risk men, that number is probably going to go up. Of those that fail surgery and go on to have salvage radiation, about half of them will eventually start to develop a rising PSA again after salvage radiation.

What is a genomic classifier?

Dr. Freedland: The term genomic classifier (GC) is specific to Decipher. More broadly, genetic tests are on the order of Prolaris, Oncotype DX, or Decipher. We use the

> *"With each successive line of treatment, the success rates go down."*

CAPRA-S, Stephenson postoperative nomogram, and similar nomograms, to make the best use of the clinical variables that we have available to us.

Is Decipher used to predict recurrence after initial prostatectomy, recurrence after salvage therapy, or both?

Dr. Freedland: Both.

Is Decipher used to predict recurrence after all types of salvage therapy or just after salvage radiation?

Dr. Freedland: It has been studied primarily after salvage radiation. Really, there aren't other great salvage therapies post-surgery other than salvage radiation. Salvage radiation is the first and foremost therapy that we use. The nice thing about the genomic data you get from GenomeDx, the company that offers Decipher, is they're now looking at predictors of responsiveness to radiation therapy in general, and to hormonal therapy, so that you actually get a lot of information, not just the

"Decipher is really ordered when a doctor isn't sure what to do."

Decipher score when you run their genomic test.

How accurate is Decipher at predicting recurrence after salvage therapy?

Dr. Freedland: It is very accurate. In terms of predicting who develops metastatic disease, it is about 85% accurate, which is pretty high compared to most of the other predictors that we have.

Let's say a man gets the Decipher test after his prostatectomy and it predicts a high possibility of recurrence. What do you do? Do you initiate salvage therapy earlier? Monitor him more carefully?

Dr. Freedland: Presumably, if you order Decipher, it is because you're not sure what to do. If the patient had very low-risk features or you found margin-negative Gleason 6 disease, you generally wouldn't order Decipher. If the patient has Gleason 10 disease, seminal vesicle invasion, and extensive positive margins, you're probably not going to order Decipher: you would radiate and be aggressive. Decipher is really ordered when a doctor isn't sure what to do.

"What is the point of knowing that someone is at risk if you're not going to do anything differently?"

There are no randomized trials that say if a man has a high Decipher score and you radiate, survival will improve. This is all based upon retrospective studies. Our best evidence implies that a high Decipher score suggests earlier radiation rather than later is better and that we should consider systemic therapy along with that radiation. For those with the highest of high Decipher scores, really novel systemic therapies [should be considered.]

"Our best evidence implies that a high Decipher score suggests earlier radiation rather than later is better."

Our standard radiation even with hormones isn't doing the trick in this scenario. We saw in our study (*Eur Urol.* 2016 Jan 21. pii: S0302-2838(16)00059-2) that for those with the highest Decipher scores, despite having had hormonal therapy and radiation in the salvage setting, over 30% of men had metastases after five years. It really speaks to the fact that these patients have a very aggressive biology and are very high risk. We really need to be thinking outside the box.

Is Decipher widely used now as a tool for predicting recurrence?

Dr. Freedland: Use is slowly increasing. I think the data are quite compelling but, like anything, it takes time to diffuse. If your doctor's bias is that he or she doesn't care what the test says, he or she is going to wait to decide on radiation, then there's really not

"We have zero data that once you know one genetic test score, knowing a second adds any value."

value in getting Decipher. What is the point of knowing that someone is at risk if you're not going to do anything differently? You need to be open to the idea of using this information to treat patients more aggressively.

Is there anything else that you think patients should know about Decipher or about predicting recurrence after salvage therapy?

Dr. Freedland: I think it's a good test. More and more, insurances and Medicare are covering it, but Decipher is not universally covered.

Is the test expensive?

Dr. Freedland: The test itself is about $3,000 or $4,000, but insurance companies often pick up the majority of that fee. There may be financial implications for the patient that should be discussed.

Do you think it makes any sense for a man to use multiple genomic tests?

Dr. Freedland: I think one test gets you the information you need. My bias is that Decipher is the most accurate of the tests out there and that it gives you the information you need.

We have zero data that once you know one genetic test score, knowing a second adds any value. I'm not saying it doesn't, just that we don't have any data to suggest it does. Pp[1]

E. David Crawford, MD
Salvage Cryotherapy

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.

Prostatepedia spoke with him about salvage cryotherapy.

How do you know a man's cancer has started growing again after treatment?

Dr. Crawford: We use rising PSA to determine biochemical failure. Every year, 60,000 to 80,000 men in the United States have biochemical failure, meaning their PSA is going up after a definitive local therapy.

Biochemical failure is an increase from a nadir PSA, which is the lowest point the PSA reaches. It used to be the nadir PSA and three consecutive rises—the PSA after radiation goes down to 0.5 and then starts going up in three consecutive tests. What that ends up meaning is that, if you're a urologist, you can order a PSA every week and see three rises in three weeks or you can order one every two years and see three rises in six years. That whole definition of three consecutive rises is in the eye of the beholder and dependent on how often you do the PSA test. So they came up with a newer definition: nadir PSA, or the lowest level, plus 2. That is called the Phoenix definition.

When someone's PSA starts rising, one of three things is going on: 1) he has a local recurrence; 2) he has a distant recurrence; or 3) he has both a distant and local recurrence. Imaging helps figure out which it is.

There are a lot of reasons for someone to fail radiation therapy: inadequate dose of radiation, inadequate application of radiation, inadequate seed implants, etc. There is also a very small subset of men who are radio-resistant—they don't respond to radiation therapy. I've seen a handful in my entire career of taking care of men with prostate cancer. They get radiation and it doesn't do anything to their tumor. Pretty rare, but it happens.

If you suspect someone has a local recurrence after radiation, what is the first thing you do? You rebiopsy the prostate. But you can still miss small cancers with biopsies. And if you have a high-grade cancer, you can have metastatic disease with a PSA of 1 or 2. This is why you do CT and bone scans at the minimum.

There are also some newer imaging techniques. I'm excited about Choline and Acetate PET/CT, but they're not readily available. Many clinicians are excited about the Axumin (fluciclovine F 18), which was approved three months ago. The advantage of Axumin is that you don't have to have a cyclotron in your backyard.

> *"Every year, 60,000 to 80,000 men in the United States have biochemical failure."*

The idea behind using imaging in this setting is the thought that maybe we are missing some distant micrometastatic disease.

What kinds of treatments are available for someone whose cancer has started growing again after radiation?

Dr. Crawford: If somebody has a recurrence after radiation therapy, the first thought is do you give more radiation? Some people do that. I don't agree with that approach, though. They failed the first time, so why do it again?

Salvage prostatectomies after radiation have a higher rate of

incontinence, almost 100% erectile dysfunction, and a higher rate of rectal injuries.

Is there a higher rate of complications because of preexisting side effects from initial radiation therapy?

Dr. Crawford: The biggest thing is that there is so much scarring from the radiation. It makes the surgery difficult.

What about salvage cryotherapy?

Dr. Crawford: If you do a mapping biopsy [see *Prostatepedia* October 2016 for an interview with Dr. Peter Pinto about MRI ultrasound fusion biopsies] and know exactly where the tumor is, you don't have to treat the whole prostate. For almost two decades, people have been doing salvage cryotherapy. In cryotherapy, you freeze the prostate. You get the tissue down to negative 40 or 30 and then freeze, thaw, freeze, thaw it until you destroy it.

The nice thing about cryotherapy is that it is minimally invasive. It's an outpatient procedure. But the urologist needs to be good at it.

The side effects of salvage cryotherapy aren't really that bad. Erectile dysfunction can be pretty high if you freeze both sides and both nerves. The good thing about cryotherapy is that it does not cut the nerves like surgery or damage them like radiation, in some people the nerves can grow back over a period of a year and a half.

Incontinence with cryotherapy is unusual—it is certainly there, but it isn't significant.

The other main risk is a fistula in the rectum. A fistula is a hole in the prostate that weakens the rectal wall,

so urine leaks into the rectum. That is not a good thing. It's rare, but it can happen. You're essentially playing chicken with the rectal wall with the cryotherapy. You have to do it right.

Cryotherapy is like anything you do: if you have a urologist who doesn't have a lot of experience, he or she is not going to do it well. There is an art to cryotherapy.

But there are plenty of data now on salvage cryotherapy, but you have to catch patients early. There has been a lot written in the COLD Registry. (The COLD registry is where urologists register their cryotherapy cases.) Jones et al. from the Cleveland Clinic have data-mined that registry.

Are treatments for those side effects effective?

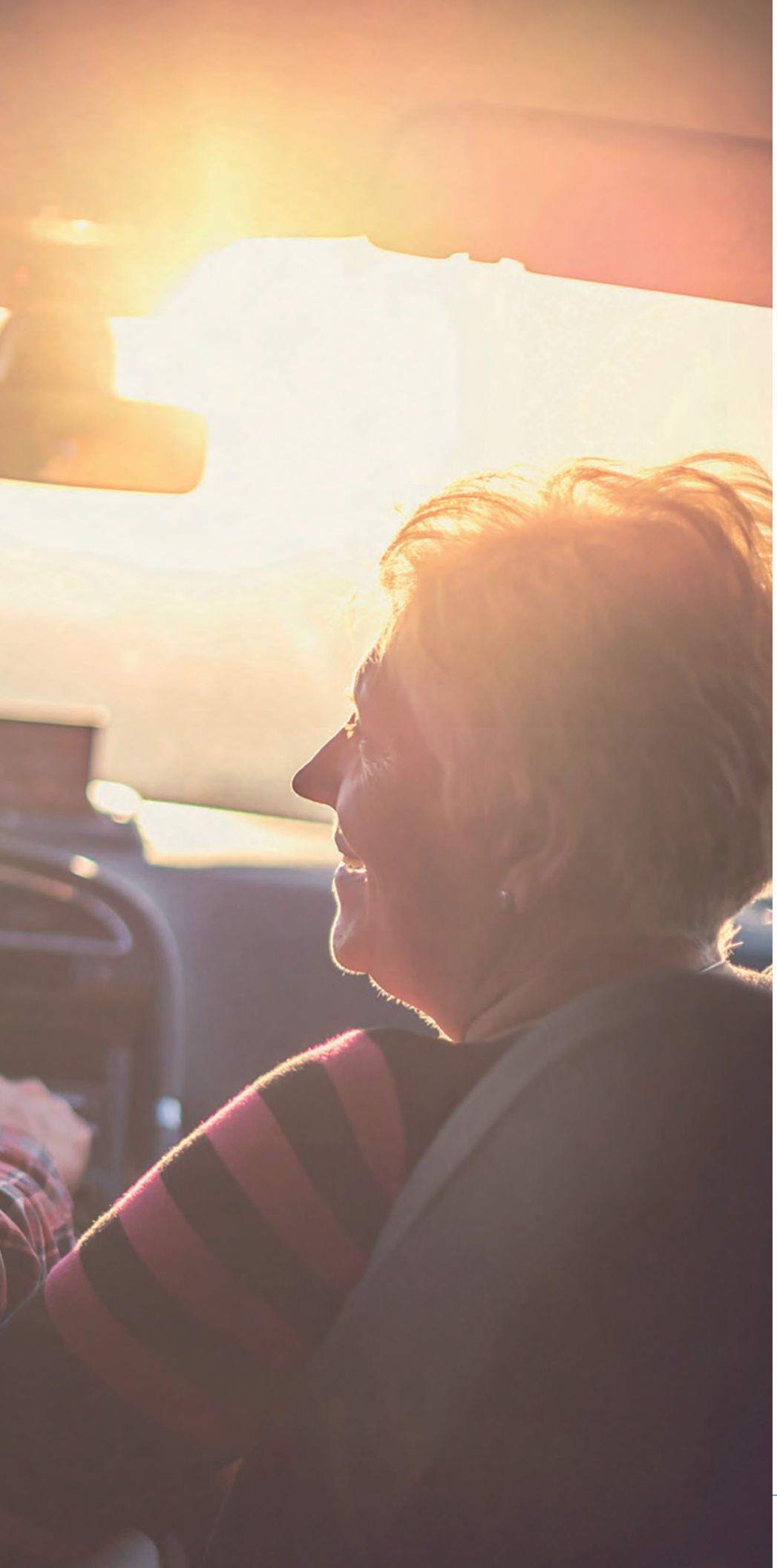
Dr. Crawford: If you leave a catheter in for a long time, sometimes the fistula will heal. Or, there is a minor operation: you go in transrectally to swing a flap up and cover the hole.

Incontinence rates are pretty low. People sometimes have urge incontinence from radiation damage to their bladder. When you take away an obstruction—like the prostate—they have uninhibited contractions of their bladder. There is no buffer and it squirts right out. You're removing that natural barrier.

Is HIFU ever used in a salvage setting?

Dr. Crawford: Yes, the other approach that is catching a lot of interest is HIFU, or high-intensity focused ultrasound. There have been some studies in the United States using salvage HIFU. It's an option. I think right now, cryotherapy is better then HIFU.

There will be other approaches, too. I think immunologically, you can get antibodies against PSMA (prostate-



specific membrane antigen) or hook it up to a radioisotope.

I was just talking to Dr. Oliver Sartor. He was telling me about a place in Heidelberg, Germany, that is using PSMA in imaging. They are hooking it up with a radioisotope and treating. They have had unbelievable responses in advanced prostate cancer.

"There is an art to cryotherapy."

Right now, though, we use either salvage cryotherapy or salvage prostatectomy if you catch patients early. You have another chance at curing them with salvage therapy.

Would you suggest that a man considering salvage cryotherapy find someone who has done a lot of this type of procedure?

Dr. Crawford: Absolutely. I think you need to have salvage cryotherapy done by somebody who does it a lot. Cryotherapy had a bad start in the United States and had a bad image for a while. Now the machine is better and the monitoring is better, so cryotherapy is better.

There was a Canadian study done looking at radiation therapy versus cryotherapy for the newly diagnosed. They found that cryotherapy was equivalent to radiation. Others argued, "Well, maybe there wasn't enough radiation." But it is an alternative, I think. Cryotherapy is underutilized. Pp'

Clinical Trial: Phuoc Tran, MD, PhD Salvage Radiation Clinical Trials

Dr. Phuoc Tran, the Clinical Director of Radiation Oncology at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, treats patients with genitourinary cancers. He uses stereotactic radiation techniques (such as SRS and SBRT/SABR) to treat patients with oligometastatic disease.

Prostatepedia spoke with him about two clinical trials he is running.

How did you come to focus on prostate cancer?

Dr. Phuoc Tran: I'm a physician/scientist: an MD/PhD with a focus on cancer biology. That interest stems all the way back from medical school through graduate school into my residency training in radiation oncology and my postdoctoral fellowship training in cancer biology. Along the process of that training, I had a chance to interact with men who had prostate cancer, which influenced greatly my research interests in prostate cancer. Despite many recent advances, prostate cancer is still among the major causes of death.

"Prostate cancer is a disease spectrum."

What is the thinking behind your Movember-PCF-funded clinical trial looking at stereotactic body radiation therapy (SBRT) in oligometastatic disease?

Dr. Tran: Cancer is not one illness, as many people believe, but many. Prostate cancer is not unique in that regard. Prostate cancer is likely broken up into distinct molecular subsets with distinct biologies and possibly distinct clinical behaviors. However, clinically speaking, we prescribe treatments for men with prostate cancer as though prostate cancer presents in discrete clinical states: in one state are patients we believe to have purely localized disease and they are curable by surgery or radiation. In the other state are patients with metastatic disease and those patients are treatable but not curable with our current therapies.

In general, this old treatment paradigm says that patients who have localized disease benefit mostly from local therapies like surgery and radiation and very little from systemic treatment like hormones and chemotherapy. Those who have metastatic disease benefit from treatments that go everywhere—hormone treatments and chemotherapy-type treatments. These patients don't benefit a lot, at least in a life-prolonging way, from radiation.

In reality, prostate cancer is a disease spectrum—with purely localized prostate cancer patients on one end and widely metastatic prostate cancer patients on the other. Within that spectrum are patients who have oligometastatic disease: low-volume metastatic disease, or just a few metastases. (Oligo is just a fancy word for *few*.) Using the same characteristics and rationale, it stands to reason that patients with limited metastatic disease might benefit from both systemic and *local* treatment. Systemic treatment to kill stray cells that may reside throughout the body, but also localized therapies to the few areas of disease that can be seen on imaging or physical exam. These oligometastatic patients actually may still be curable because some, myself included, believe that they are closer in disease biology to localized patients than widely metastatic patients. Right now, as I previously stated, the old way of thinking is that a patient is not curable whether he has one or 100 metastases.

There is some provocative data, but a lower level of evidence—what we call *retrospective* data—which suggests this approach of giving local therapy to those with only a few metastases may be true. If you treat not only the primary disease in the prostate or the pelvis, but also the few metastatic lesions, patients can actually live a long time without disease progression and/or be cured.

> *"There is data suggesting there may be a benefit from local therapies like surgery and radiation to oligometastatic patients."*

In colorectal cancer, for instance, when just a few lesions have gone to the liver, the treatment paradigm is to give chemotherapy, surgery to remove the colorectal cancer, as well as intensive local therapy to those liver metastases. A fair number of patients can be cured. It's not that unreasonable to extend this idea to prostate cancer patients.

From a radiation oncology perspective, there has been a lot of technological growth over the last 15 to 20 years, which has culminated into an approach called stereotactic body radiation therapy (SBRT) or stereotactic ablative radiation (SABR). SBRT and SABR are highly focused radiation given in an intense fashion. I tell patients it's like spot welding—small area, very intense, and theoretically ablative, meaning it kills all the cancer in that spot.

Armed with that new technology and with the idea that local therapies such as surgery, radiation, and other ablative therapies can be beneficial in oligometastatic patients, we wanted to test our idea in a rigorous way. There is data suggesting there may be a benefit from local therapies like surgery and radiation to oligometastatic patients, but there is not, at least in prostate cancer, good data from randomized clinical trials.

Our trial is a randomized trial of patients with oligometastatic prostate cancer defined as three or fewer metastases. They have to have received treatment for the primary prostate disease, so surgery or radiation, and have had no prior hormonal therapy for their metastatic disease. They can have had hormonal therapies in conjunction with treatment for their *primary* disease, but not for their *metastatic* disease.

Patients are randomized to either SABR to up to three sites or a short observation period of three to six months. The randomization is 2:1 to SABR versus observation.

Are there any other eligibility requirements?

Dr. Tran: Like I said, the number of lesions has to be three or less. The tumors have to be of a certain bulk or size—they can't be too large. Patients have to have a PSA doubling time of less than 15 months. (PSA doubling time is the time it takes for the PSA to double.) We chose less than 15 months because there are patients who have biochemical failure or low-volume metastatic disease with long doubling times, sometimes many years. Those patients, frankly, probably just won't ever need to be treated. We want to zero in on patients for whom this type of treatment can make a difference.

Why do you limit to three mets? I thought oligometastatic disease was defined as three to five?

Dr. Tran: The definition of oligometastatic disease depends on the histology, so it is different for prostate versus lung cancer versus other cancers. In general, the literature defines oligometastatic disease as three to five mets. In prostate cancer, there is not a terrific amount of good data. But because we're doing a randomized trial with an observation component, we wanted to limit the number of mets to three for safety reasons.

Do patients need to be in the Baltimore area to participate?

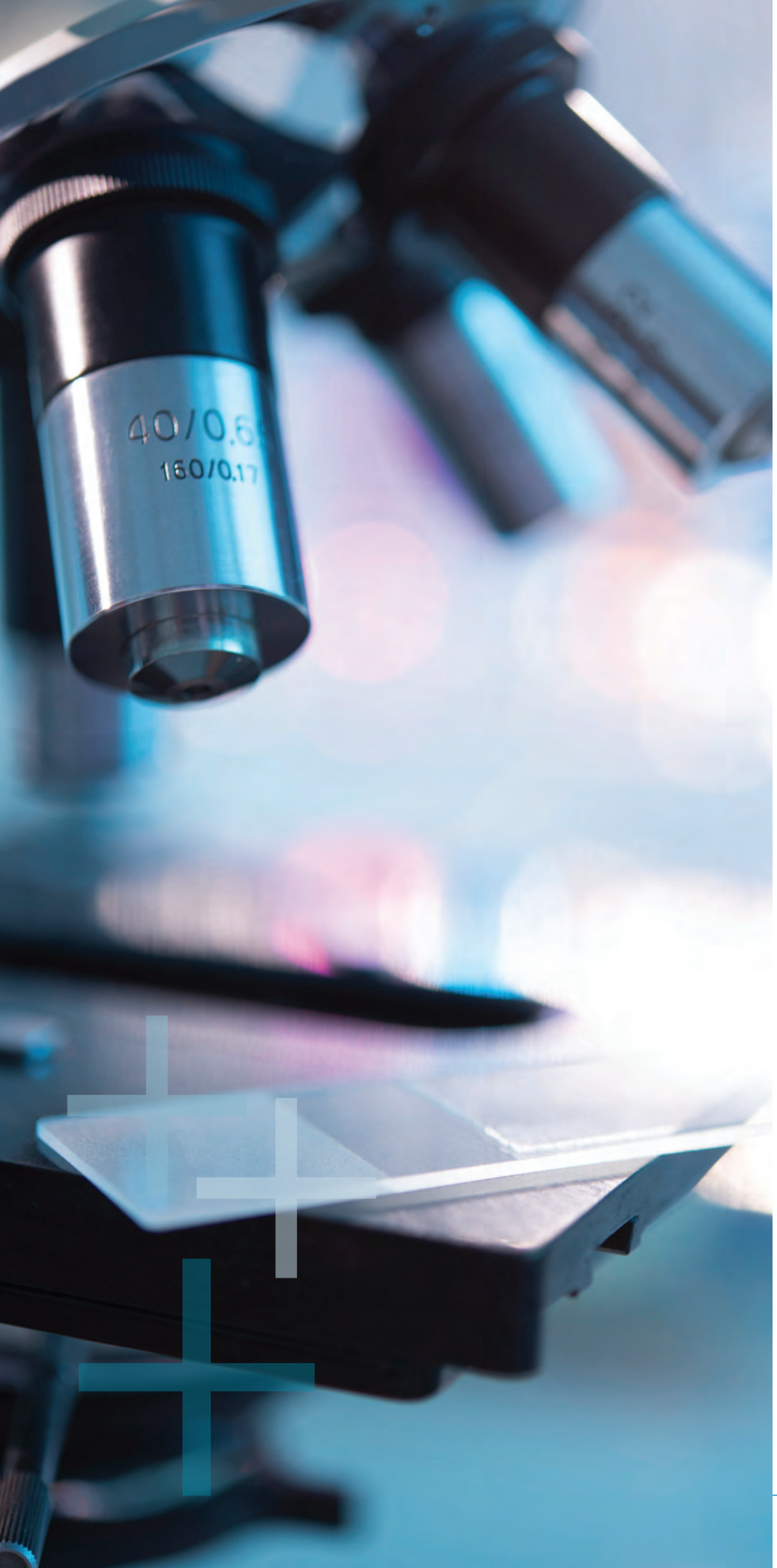
Dr. Tran: The fortunate thing with this trial is that because we're using SABR we can treat individual lesions in anywhere from one to five treatments, unlike traditional radiation that requires eight weeks. If patients come to Baltimore for treatment, it wouldn't have to be for as long as traditional conventional radiation.

We are thinking about opening up the trial at sites outside of the Baltimore/Washington area, but we haven't made that jump yet.

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

Dr. Tran: We're going to have a lot of really interesting correlative studies. Patients will have their blood drawn before treatment and at three and six months. We'll be using those blood samples to look at things like circulating tumor DNA and circulating tumor cells.

We're also going to look at the effect of radiation on the immune system, by looking at something known as T-cell receptor profiling, which is



a really advanced way to look at individual circulating T-cells.

We will also look at a new PSMA-based radiotracer called DCFPyL. PSMA is a marker commonly displayed on prostate cancer cells that allows us to employ a very sensitive type of imaging. Patients will get that as well so that we can evaluate how helpful that imaging is.

Our study is trying to answer whether or not we can change the natural history of oligometastatic disease with SABR while also evaluating cutting-edge correlative and translational science endpoints.

How many patients will you enroll?

Dr. Tran: This is a 54-patient trial: 36 patients will be randomized to the active treatment arm and 18 to the control arm. In the observation arm, if a patient progresses—typically measured by PSA—he can cross over and get SABR off-trial. Ultimately, all patients can be treated with SABR.

Do you have a second trial that combines salvage radiation therapy with Xtandi (enzalutamide)?

Dr. Tran: Yes. About 30,000 men die of metastatic castration-resistant prostate cancer every year. Only about a third, or 10,000, are diagnosed initially with metastatic prostate cancer. The majority of the patients who die every year had, at initial diagnosis, actually presented with localized disease that was potentially curable. They were treated with surgery or radiation, but these therapies, unfortunately, didn't work.

These men recur biochemically in most cases, meaning their PSA starts going up. Up to two-thirds of these men then progress farther and farther down this unfortunate pathway until

they have metastatic castration-resistant prostate cancer. If we had something better in the way of salvage treatment, those men could potentially be spared that progression to metastatic castration-resistant prostate cancer and ultimately death.

Salvage radiation is standard of care for patients who have failed surgery and have biochemical failure. Unfortunately, for a number of reasons, it's not as effective as we'd like. In certain patients, salvage radiation can be quite effective, as high as 70 to 80%. But if we lump all the patients together whom we treat with salvage radiation, we only have about a 40 to 50% control, or success, rate. Bottom line: we need to improve that.

If we had much better salvage treatments, perhaps we could get the number of men who die every year down to as low as 10,000. Recall that the majority of men who die from prostate cancer each year originally had potentially curable disease. That is the basis of our study: trying to reach the biggest population of patients to whom we can potentially give a second chance at a cure.

We know from patients presenting with prostate cancer who are treated with radiation upfront that radiation can have a synergistic interaction with hormone deprivation or hormone therapy. There are many Phase III trials demonstrating this with excellent data. Some of the best data in prostate cancer in general shows that radiation combined with hormones cures more men.

Unfortunately, in the salvage setting—that is when men have biochemical failure after radical prostatectomy—there is very little in the way of good randomized data. As I said before, there are a huge number of men with prostate cancer who fall into that space. We want to improve outcomes of men in this space in a scientifically rigorous way.

"Patients are given salvage radiation and receive either a placebo or Xtandi (enzalutamide)."

A medical oncologist named Dr. Emmanuel Antonarakis and I led the design and activation of a trial called SALVENZA, which is a Phase II randomized trial of men with prostate cancer with biochemical failure following radical prostatectomy. Patients are given salvage radiation and receive either a placebo or Xtandi (enzalutamide).

Xtandi (enzalutamide) is, as I'm sure many of your readers know, a next-generation hormone blocker, which has been FDA approved for use in metastatic castration-resistant prostate cancer, both pre- and postchemotherapy. There are also some very promising new studies that are now being reported looking at Xtandi (enzalutamide) in the rising PSA castration-resistant prostate cancer space. Xtandi (enzalutamide) also has a very promising side effect profile compared to traditional castrating hormonal therapy, which knocks testosterone down to less than 20.

In that trial, the hope is that we'll be able to increase the ability of salvage radiation to cure more men by adding Xtandi (enzalutamide) and test this concept in the most rigorous way possible by randomizing men to Xtandi (enzalutamide) and placebo control.

Is that trial also Baltimore-based?

Dr. Tran: This is a multi-institutional trial open at Johns Hopkins University, as well as the University of Michigan, Wayne State University, the University of Chicago, the University of Utah, and Oregon Health Sciences University. We're trying to open at the University of Texas Southwestern in Dallas as well.

Are there any eligibility criteria?

Dr. Tran: We're looking for men who have biochemical failure following radical prostatectomy. They have to have a Gleason 7 with positive margins or extracapsular extension following surgery or a Gleason 8 to 10. They have to have a detectable PSA, obviously, on two subsequent determinations, so a PSA of 0.1 twice.

How many patients will you enroll?

Dr. Tran: It is a 122-patient trial. We're about a third of the way there, but we need to finish enrolling in the next year or two. Pp[1]

How To Get Involved…

Patients who are interested in participating should contact Dr. Tran at 410-502-8000 or tranp@jhmi.edu for more details.

Mr. Jonathan Levy
Patient Helplines + Conferences

Jonathan Levy, a recurrent prostate cancer patient, offers support to other men through the Prostate Cancer Research Institute's popular Helpline (http://pcri.org/ or (800) 641-7274) and support groups at biannual patient conferences.

Prostatepedia spoke with him recently about his prostate cancer journey and the work he does with PCRI.

How did you find out that you had prostate cancer?

Mr. Jonathan Levy: In 2007, I had a PSA of 4. I had a biopsy; it was negative.

Three years went by. They were already starting to slow down on prostate cancer screening. And then I had a physical and thought, "I haven't had a PSA taken for three years."

"Everybody was crying —my daughter, me."

So we tested my PSA and it came back 32.

I went to see a urologist and had another biopsy: I had a Gleason 7 (3 + 4). They also did a CT and found a liver metastasis. This wasn't just a diagnosis of early, localized prostate cancer. He was telling me I already had liver metastases.

I went home in complete shock. Everybody was crying—my daughter, me. I called a physician friend. He ends up giving me some very useful information about it—he said, "You know, liver metastases are really rare." That bit of advice got me thinking. I started to research. Liver metastases are really rare. Why would I have this thing? The research says to get a biopsy. They won't do the biopsy—given where it was, it is just too dangerous. But they do a different CAT scan with a different technique and that liver metastasis turns out to be a benign hemangioma.

Of course, I lose complete trust in this urologist. I found another urologist and ended up with radiation and a couple of years of hormone therapy. My PSA was zero for a while.

Then it started creeping up again—so I had a recurrence. The question was: where was it recurring? I had a Choline PET/CT scan. I had a mapping

biopsy. Nobody could find the recurrence. My PSA kept going back up to 10 then 20 then 25. When the PSA got up to about 30 it finally showed up on a F18 Sodium Fluoride PET bone scan: four or five spots.

"Everybody who comes to these conferences has a nagging idea … that this is not the end of the story."

I had already found out about a clinical trial, which I've now been on for two years. At the moment, everything is good. PSA is undetectable. New bone scan shows regression. I'm in remission.

What is the trial?

Mr. Levy: The trial is using Lupron and TAK-700, an experimental drug, which is now being used on men who are hormone-sensitive and metastatic. There are only a few trials around like that. There are about 1,600 men on the trial.

How did you become involved in prostate cancer support and outreach?

Mr. Levy: I was shocked and confused and then I found Prostate Cancer Research Institute (PCRI). I called their helpline and that was the beginning of this whole journey. They gave me some background information, helped me understand my Gleason score, helped me understand what my treatment options would be, and gave me support.

I did go to a support group. But for me, this was better. The support group is different. The Helpline had more evidenced-based information.

Every few months, I'd call back. Once I was treated and everything looked okay—my PSA was zero—they asked, "What do you think about joining the Helpline?" PCRI felt I had the potential to do the work. I started training.

When did you attend your first patient conference?

Mr. Levy: I didn't go to my first true conference until much later. I had a very independent approach. I knew what I wanted to do and I just did it. Then, if it didn't work out, I did something else. That was how I kept approaching it. I always checked back with PCRI and told them what had happened. I wasn't too involved until I got involved.

"Look for good information."

By the time I got to a conference, I was already working on the Helpline. I had been doing this kind of work and knew how helpful it could be.

At the conference, they have lectures, question-and-answers with the doctors after their lectures, and support groups.

Which of those different formats did you find most helpful?

Mr. Levy: All! I run a support group for recurrence at all of the conferences now. I try to attend as many of the presentations as I can.

Sometimes I meet someone in the hall and they say, "Hey, I spoke to you on the phone!" And then for half an hour we stand talking about things. It's like the Helpline but in person.

But I think the support groups that I run, to me, are the most alive.

Men come from all over. That is where it really gets real. They're there with their wives and girlfriends.

Why do you think it's important for patients to attend conferences like the ones PCRI runs if they've already been treated?

Mr. Levy: Some men, they get treated and that is the end of the story. They don't want to know anymore. And some men don't want to know even before they're treated.

But there are some people who want to know more. Everybody who comes to these conferences has a nagging idea that he is going to need to know something in the future, that this is not the end of the story. They have that idea in the back of their minds, "I might need to know about these things in the future because the recurrence rate is pretty high."

So then the more you know when it does come back, the better off you'll be?

Mr. Levy: I think so. A lot of the people who come are men who have been treated but have no sign of recurrence. They still come, so what brings them? They have this need to know and participate.

What do you think about the notion of a prostate cancer community?

Mr. Levy: I have relationships with some that have grown to be very close.

More Information…

http://pcri.org/helpline-resource-center/#helpline-resource-center-home

One guy came down here to have lunch with me. A doctor I know is treating another person. He finds me at the prostate cancer conference and wants to talk. This was the first time we'd ever met.

There is an intimacy that develops between patients that they don't always get from their doctors.

"The question was: where was it recurring?"

Sometimes, they don't get that intimacy from their spouses either. It's a community that they feel a part of.

It's a strange thing, a community based on a disease and everything that it brings with it. Still, it brings people together.

I suppose it's a type of brotherhood?

Mr. Levy: Definitely a kind of brotherhood.

What about men who can't attend the patient conferences?

Mr. Levy: To me, the Helpline is the core. That is the foundation. They've just been diagnosed. They're frightened. They're confused.

I can relate to that. You don't know what is going to come popping out. It could be anything. It could be worry about a sexual relationship. It could be, "How long am I going to live? When am I going to die?" That comes up a lot. It could be, "What about this drug they put me on? I don't want to go on hormone therapy. I'm going to turn into a woman."

Everything just comes out as they talk. Let it all out. It's got to come out.

Do only patients staff the Helpline?

Mr. Levy: Yes. There is an office staff, but yes, everybody who actually takes calls must be a patient and have had training.

What advice would you give to a man whose cancer has come back after initial treatment or has just been diagnosed?

Mr. Levy: I tell a guy who has just been diagnosed to keep his medical records. I then go over his medical records with him. That way he can really develop a picture of what is happening. That is when men start to understand what they are facing.

A guy who has recurrence has a completely different story. He knows he has prostate cancer. Those men are often in the same situation I was in.

They want to know where the cancer is recurring because a lot of them don't even have a prostate anymore. Why is their PSA rising? The cancer is somewhere, but where? Is it worth expending a lot of effort to find it, knowing that you may never find it, or is it important to go right on to treatment? For me, the most important thing was to find it, but for other men, it is more important to jump right into treatment.

Look for good information. If you don't feel comfortable with your doctor, keep looking. A lot of people have no confidence in their doctor, but keep seeing him.

I don't want to be a caller's patient advocate. I want to see him become

"I was shocked and confused and then I found Prostate Cancer Research Institute (PCRI)."

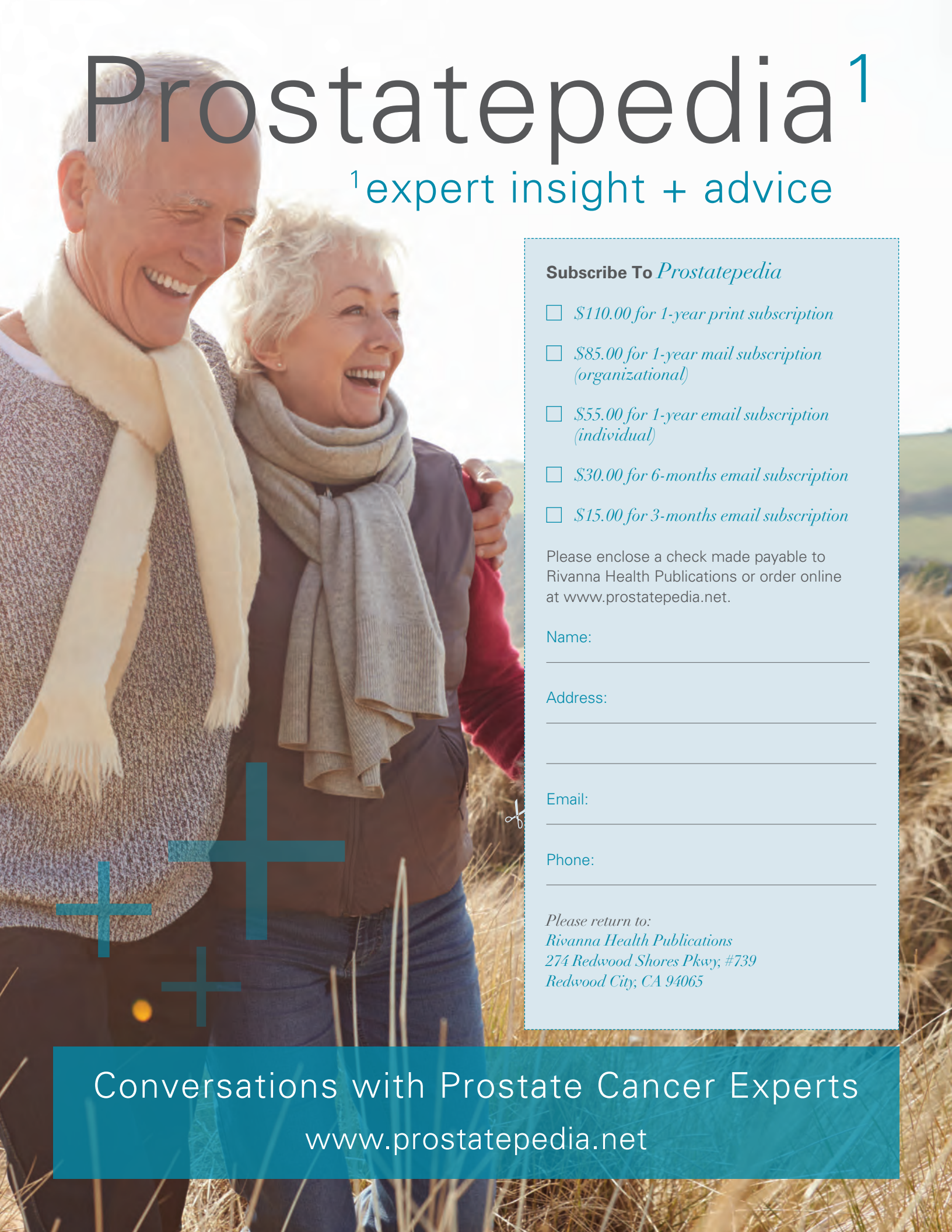
his own patient advocate, to be as informed as he can be. Otherwise, you're just a pawn. Take responsibility for what you're doing.

Do you have any advice for caregivers or spouses?

Mr. Levy: Usually it's a girlfriend or wife who calls the Helpline. A lot of times, the husband doesn't want to know anything about it. The wife is the advocate. Once in a while, the patient will get on, but sometimes never.

The hardest part is living with the cancer. Sometimes men hide it, or don't want to discuss it, or hide the fact that they're in pain. There are a lot of masculine things that come into this. It creates a lot of stress. And sometimes people get divorced over prostate cancer, too.

Burnout is a possibility. A lot of caregivers are just completely engrossed in trying to care for their husband, but you have to get out of the house and do something for yourself. If you go down, its not going to help anybody. Pp1



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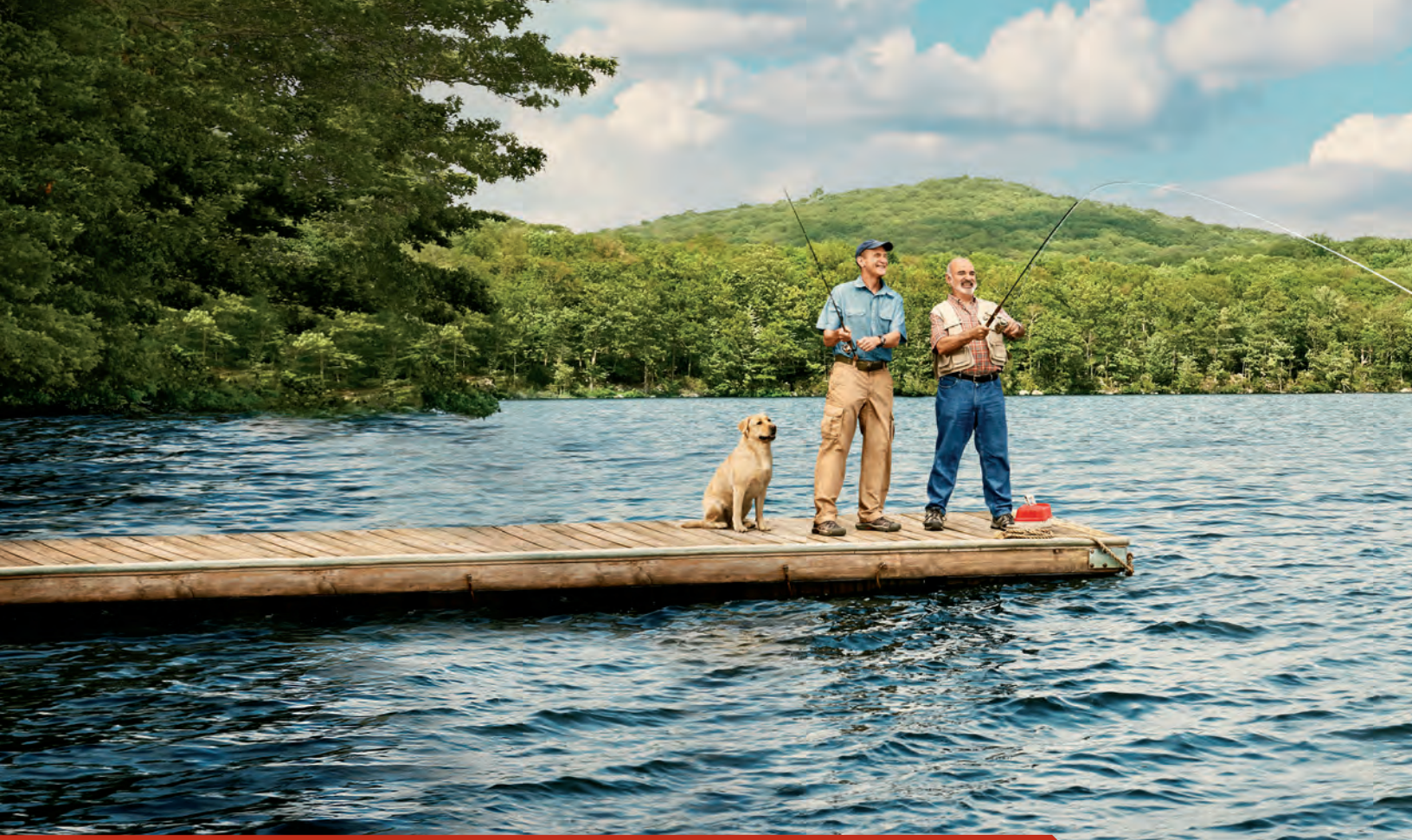

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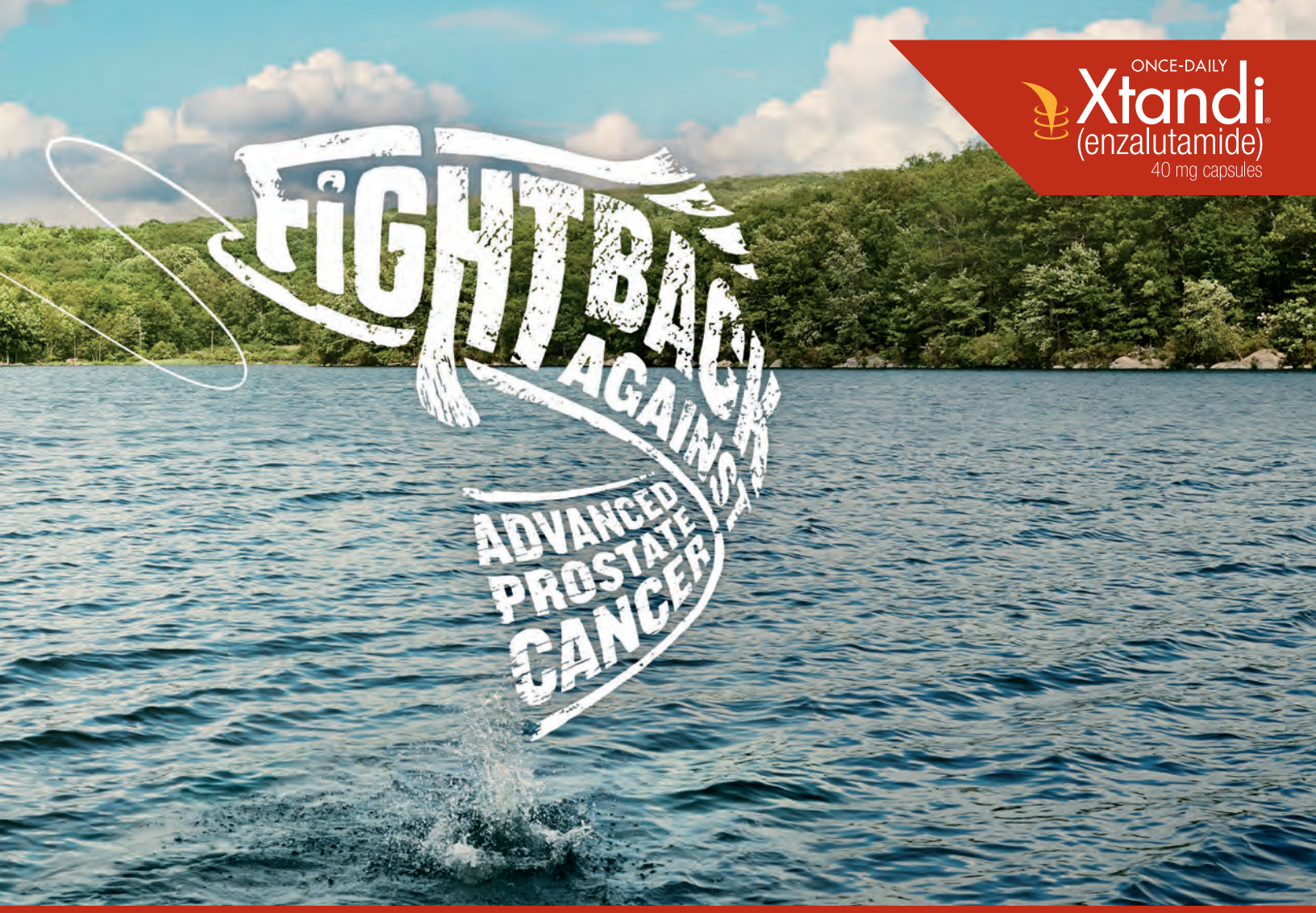
- Have a history of seizures, brain injury, stroke or brain tumors.
- Have any other medical conditions.
- Have a partner who is pregnant or may become pregnant. Men who are sexually active with a pregnant woman must use a condom during and for 3 months after treatment with XTANDI. If your sexual partner 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.

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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.

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- **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.
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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

Manufactured by:
Catalent Pharma Solutions, LLC, St. Petersburg, FL 33716

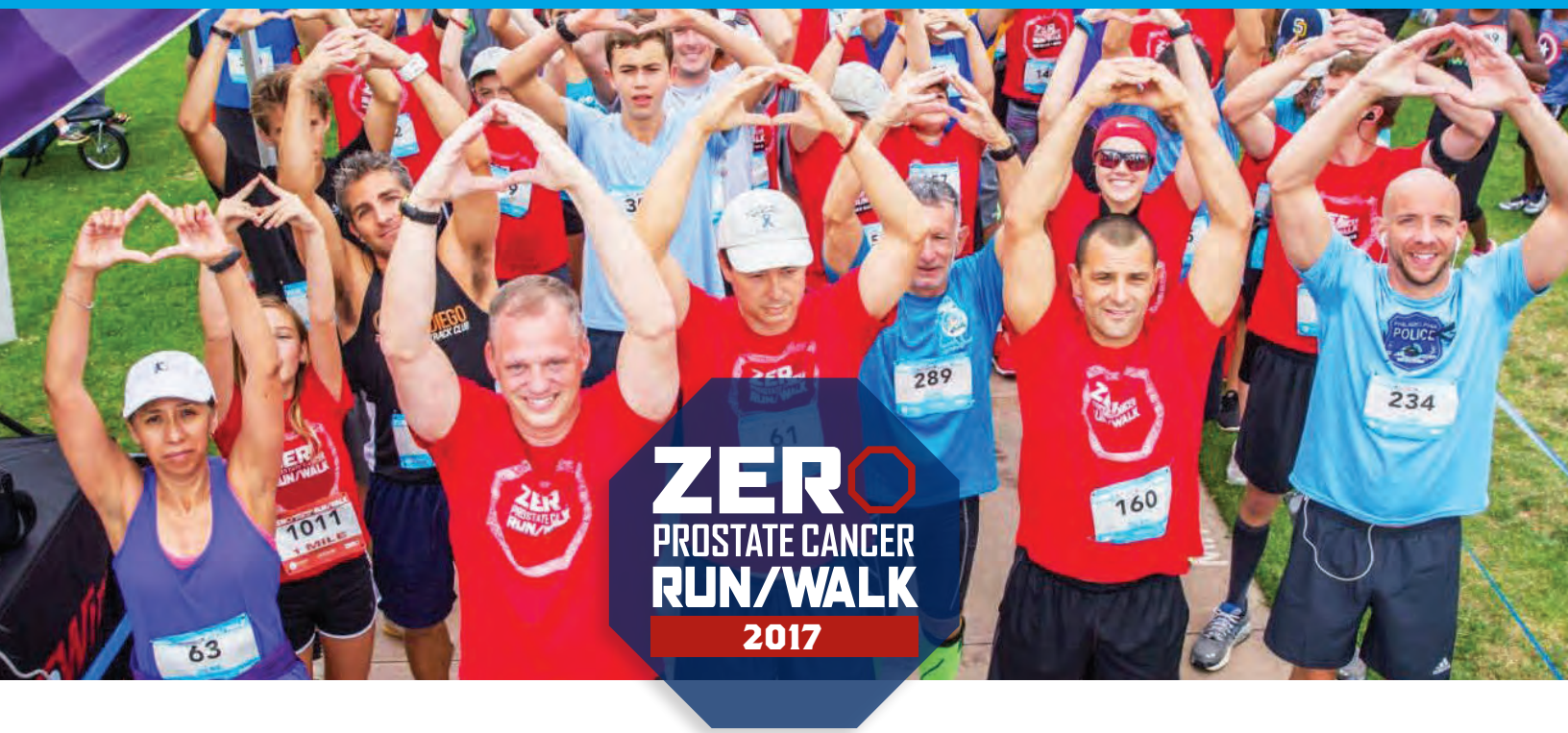
Marketed by:
Astellas Pharma US, Inc., Northbrook, IL 60062
Medivation Inc., San Francisco, CA 94105
14L082-XTA-BRFS

076-1121-PM

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

Revised: August 2015

Thank you for a great 2016! Join the fun in 2017 and help us end prostate cancer!



Support the one in seven American men affected by prostate cancer at one of these family-friendly events in 2017. Survivors and patients are the true ZERO's Heroes at our Run/Walks, and we're fighting for you. We fundraise, run, and walk in your honor in the hope that one day we will achieve Generation ZERO – the first generation free from prostate cancer.

JOIN US! www.zeroprostatecancerrun.org

Allentown, PA – August 2017
Asheville, NC – November 2017
Augusta, GA – November 2017
Austin, TX – November 2017
Baltimore, MD – September 24, 2017
Birmingham, AL – Spring 2017
Boston, MA – September 2017
Charleston, SC – October 2017
Chicago, IL – June 3, 2017
Cincinnati, OH – October 2017
Cleveland, OH – August 2017
Columbus, OH – August 26, 2017
Corpus Christi, TX – October 2017
Dallas/Fort Worth, TX – September 2017
Dayton, OH – September 2017
Des Moines, IA – September 2017
El Paso, TX – June 2017
Greensboro, NC – November 2017
Harrisburg, PA – September 2017
Hartford, CT – June 2017
Jacksonville, FL – December 2017
Kansas City, KS – October 2017
Lansing, MI – Fall 2017
Lincoln, NE – September 2017
Los Angeles, CA – June 2017
Miami, FL – September 2017
Minneapolis, MN – September 2017
Napa Valley, CA – September 2017
Oklahoma City, OK – September 2017
Portland, OR – June 11, 2017
Raleigh NC – June 24, 2017
Salt Lake City, UT – June 10, 2017
San Antonio, TX – September 17, 2017
San Diego, CA – September 2017
San Francisco, CA – November 2017
St. Louis, MO – September 16, 2017
Syracuse, NY – June 2017
Tucson, AZ – March 4, 2017
Virginia Beach, VA –November 2017
Washington, DC – June 18, 2017
Wichita, KS – June 17, 2017

WHERE THE MONEY GOES
94 CENTS OF EVERY DOLLAR GOES TO PROGRAMS & ACTIVITIES

TO BENEFIT ZERO THE END OF PROSTATE CANCER

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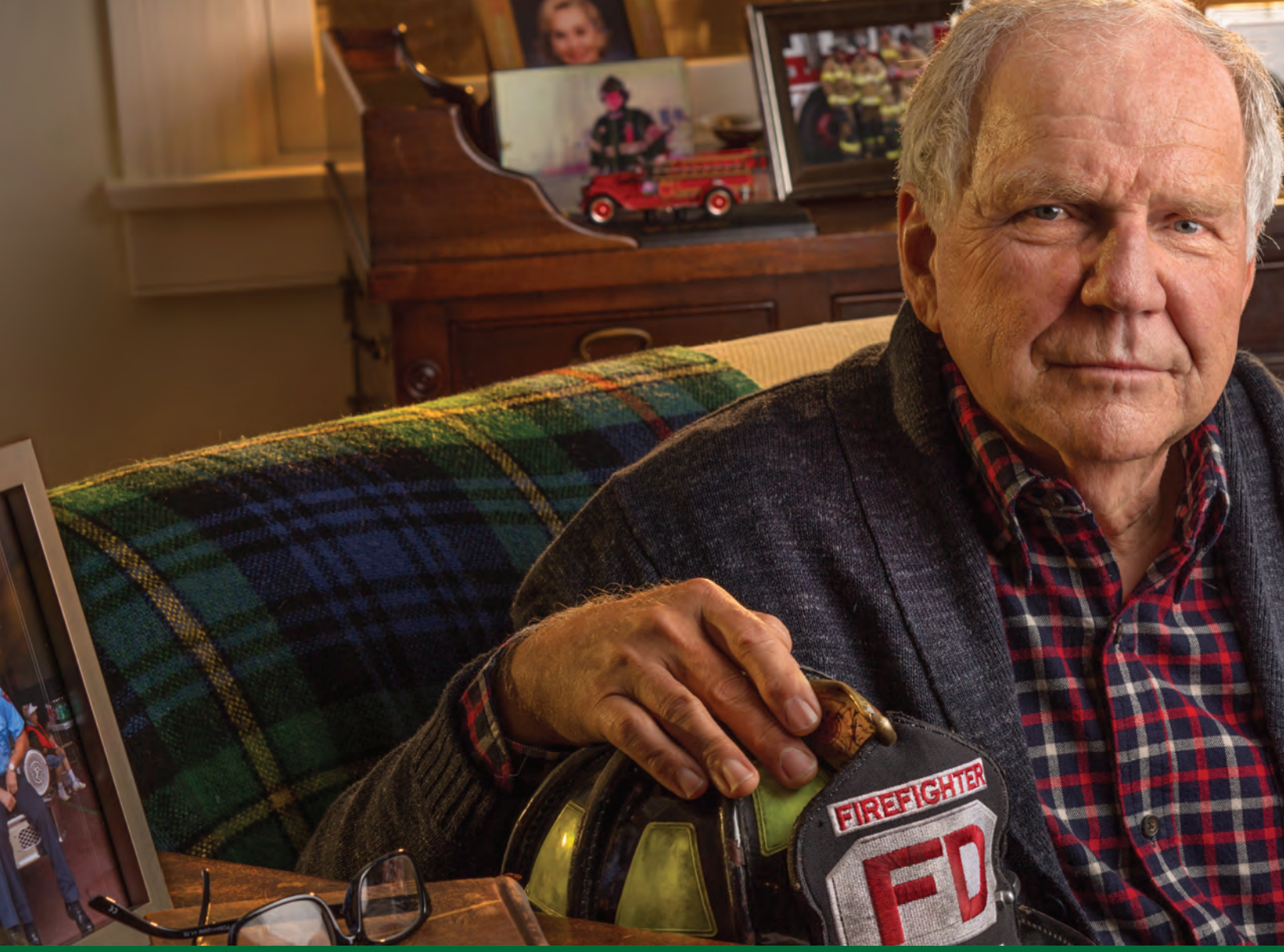


WHAT IS ZYTIGA® (abiraterone acetate)**?**

ZYTIGA® is a prescription medicine that is used along with prednisone. ZYTIGA® is used to treat men with castration-resistant prostate cancer (prostate cancer that is resistant to medical or surgical treatments that lower testosterone) that has spread to other parts of the body.

IMPORTANT SAFETY INFORMATION

Who should not take ZYTIGA® (abiraterone acetate)?

Do not take ZYTIGA® if you are pregnant or may become pregnant. ZYTIGA® may harm your unborn baby. Women who are pregnant or who may become pregnant should not touch ZYTIGA® without protection, such as gloves.

ZYTIGA® is not for use in women or children. **Keep ZYTIGA® and all medicines out of the reach of children.**

Before you take ZYTIGA®, tell your healthcare provider if you:

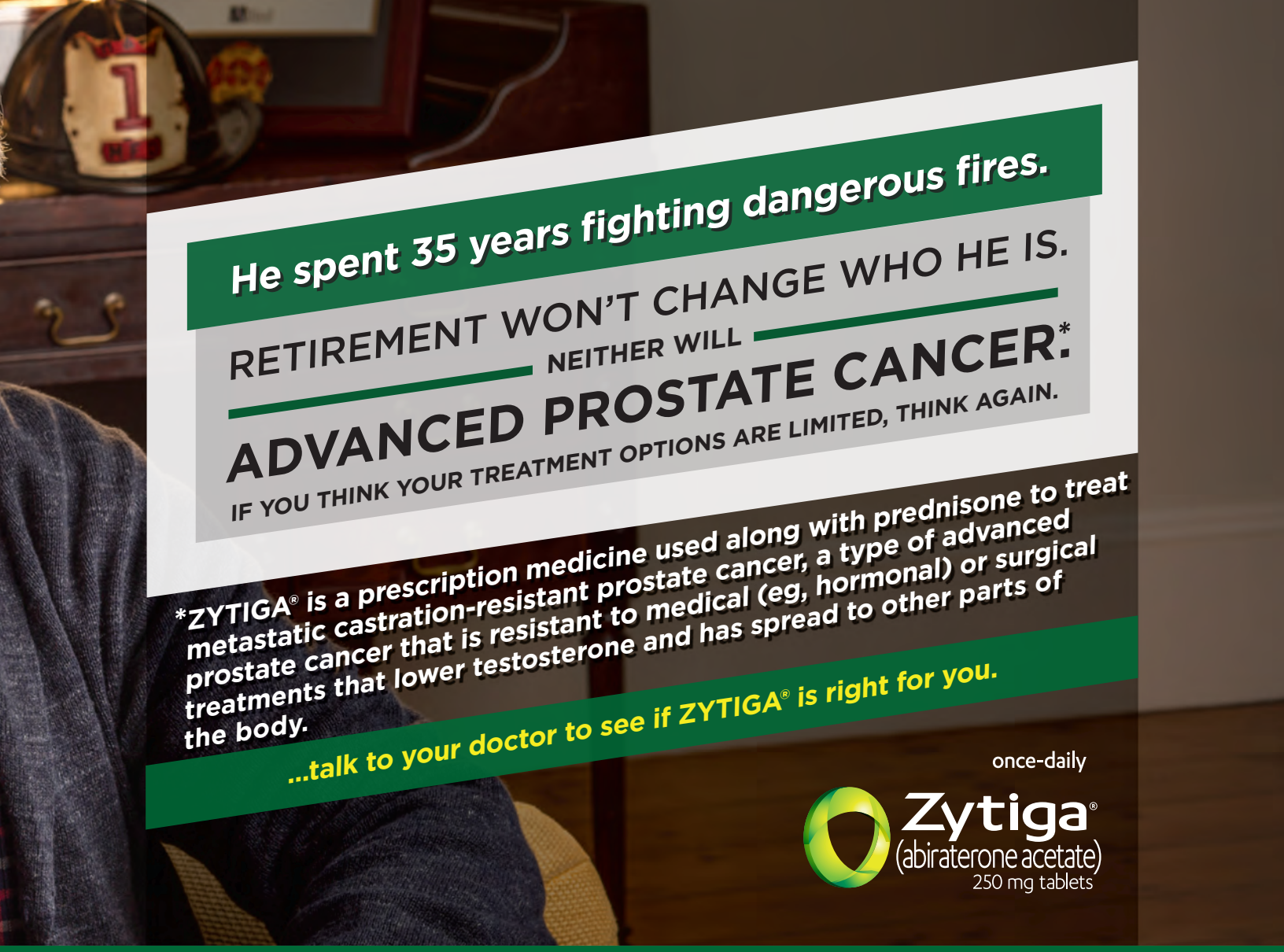
- Have heart problems
- Have liver problems
- Have a history of adrenal problems
- Have a history of pituitary problems
- Have any other medical conditions
- Plan to become pregnant **(See "Who should not take ZYTIGA®?")**
- Are breastfeeding or plan to breastfeed. It is not known if ZYTIGA® passes into your breast milk. You and your healthcare provider should decide if you will take ZYTIGA® or breastfeed. You should not do both. **(See "Who should not take ZYTIGA®?")**
- Take any other medicines, including prescription and over-the-counter medicines, vitamins, and herbal supplements. ZYTIGA® can interact with many other medicines.

If you are taking ZYTIGA®:

- Take ZYTIGA® and prednisone exactly as your healthcare provider tells you.
- Take your prescribed dose of ZYTIGA® one time a day. Your healthcare provider may change your dose if needed.
- Do not stop taking your prescribed dose of ZYTIGA® or prednisone without talking to your healthcare provider first.
- Take ZYTIGA® on an empty stomach. **Do not take ZYTIGA® with food.** Taking ZYTIGA® with food may cause more of the medicine to be absorbed by the body than is needed and this may cause side effects.
- No food should be eaten 2 hours before and 1 hour after taking ZYTIGA®.
- Swallow ZYTIGA® tablets whole. Do not crush or chew tablets.
- Take ZYTIGA® tablets with water.
- Your healthcare provider will do blood tests to check for side effects.
- Men who are sexually active with a pregnant woman must use a condom during and for one week after treatment with ZYTIGA®. If their female partner may become pregnant a condom and another form of birth control must be used during and for one week after treatment with ZYTIGA®. Talk with your healthcare provider if you have any questions about birth control.
- If you miss a dose of ZYTIGA® or prednisone, take your prescribed dose the following day. If you miss more than 1 dose, tell your healthcare provider right away.

ZYTIGA® may cause serious side effects including:

- **High blood pressure (hypertension), low blood potassium levels (hypokalemia), and fluid retention (edema).**



Tell your healthcare provider if you get any of the following symptoms:

- Dizziness
- Feel faint or lightheaded
- Confusion
- Pain in your legs
- Fast heartbeats
- Headache
- Muscle weakness
- Swelling in your legs or feet

- **Adrenal problems** may happen if you stop taking prednisone, get an infection, or are under stress.
- **Liver problems.** You may develop changes in liver function blood tests. Your healthcare provider will do blood tests to check your liver before treatment with ZYTIGA® and during treatment with ZYTIGA®. Liver failure may occur, which can lead to death. Tell your healthcare provider if you notice any of the following changes:
  - Yellowing of the skin or eyes
  - Darkening of the urine
  - Severe nausea or vomiting
- The most common side effects of ZYTIGA® include:
  - Weakness
  - Joint swelling or pain
  - Swelling in your legs or feet
  - Hot flushes
  - Diarrhea
  - Vomiting
  - Cough
  - High blood pressure
  - Shortness of breath
  - Urinary tract infection
  - Bruising
  - Low red blood cells (anemia) and low blood potassium levels
  - High blood sugar levels, high blood cholesterol and triglycerides
  - Certain other abnormal blood tests

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 ZYTIGA®.

FOR MORE INFORMATION, ASK YOUR HEALTHCARE PROVIDER OR PHARMACIST.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

ZYTIGA® can interact with other medicines.

You should not start or stop any medicine before you talk with the healthcare provider who prescribed ZYTIGA®.

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

Call your doctor for medical advice about side effects. 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 (1-800-332-1088).

051527-160418

Janssen Biotech, Inc.
800 Ridgeview Drive
Horsham, PA 19044 USA

 08/16 038767-160817

janssen

PATIENT INFORMATION
ZYTIGA® (**Zye**-tee-**ga**)
(abiraterone acetate)
Tablets

Read this Patient Information that comes with ZYTIGA before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is ZYTIGA?
ZYTIGA is a prescription medicine that is used along with prednisone. ZYTIGA is used to treat men with castration-resistant prostate cancer (prostate cancer that is resistant to medical or surgical treatments that lower testosterone) that has spread to other parts of the body.

ZYTIGA is not for use in women.

It is not known if ZYTIGA is safe or effective in children.

Who should not take ZYTIGA?
Do not take ZYTIGA if you are pregnant or may become pregnant. ZYTIGA may harm your unborn baby.

Women who are pregnant or who may become pregnant should not touch ZYTIGA without protection, such as gloves.

What should I tell my healthcare provider before taking ZYTIGA?
Before you take ZYTIGA, tell your healthcare provider if you:
- have heart problems
- have liver problems
- have a history of adrenal problems
- have a history of pituitary problems
- have any other medical conditions
- plan to become pregnant. See "**Who should not take ZYTIGA?**"
- are breastfeeding or plan to breastfeed. It is not known if ZYTIGA passes into your breast milk. You and your healthcare provider should decide if you will take ZYTIGA or breastfeed. You should not do both. See "**Who should not take ZYTIGA?**"

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. ZYTIGA can interact with many other medicines.

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

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

How should I take ZYTIGA?
- Take ZYTIGA and prednisone exactly as your healthcare provider tells you.
- Take your prescribed dose of ZYTIGA 1 time a day.
- Your healthcare provider may change your dose if needed.
- Do not stop taking your prescribed dose of ZYTIGA or prednisone without talking with your healthcare provider first.
- Take ZYTIGA on an empty stomach. **Do not take ZYTIGA with food.** Taking ZYTIGA with food may cause more of the medicine to be absorbed by the body than is needed and this may cause side effects.
- No food should be eaten 2 hours before and 1 hour after taking ZYTIGA.
- Swallow ZYTIGA tablets whole. Do not crush or chew tablets.
- Take ZYTIGA tablets with water.
- Men who are sexually active with a pregnant woman must use a condom during and for 1 week after treatment with ZYTIGA. If their female partner may become pregnant, a condom and another form of birth control must be used during and for 1 week after treatment with ZYTIGA. Talk with your healthcare provider if you have questions about birth control.
- If you miss a dose of ZYTIGA or prednisone, take your prescribed dose the following day. If you miss more than 1 dose, tell your healthcare provider right away.
- Your healthcare provider will do blood tests to check for side effects.

What are the possible side effects of ZYTIGA?

ZYTIGA may cause serious side effects including:

- **High blood pressure (hypertension), low blood potassium levels (hypokalemia) and fluid retention (edema)**. Tell your healthcare provider if you get any of the following symptoms:
  - dizziness
  - fast heartbeats
  - feel faint or lightheaded
  - headache
  - confusion
  - muscle weakness
  - pain in your legs
  - swelling in your legs or feet
- **Adrenal problems** may happen if you stop taking prednisone, get an infection, or are under stress.
- **Liver problems**. You may develop changes in liver function blood test. Your healthcare provider will do blood tests to check your liver before treatment with ZYTIGA and during treatment with ZYTIGA.

  Liver failure may occur, which can lead to death. Tell your healthcare provider if you notice any of the following changes:
  - yellowing of the skin or eyes
  - darkening of the urine
  - severe nausea or vomiting

The most common side effects of ZYTIGA include:

- weakness
- joint swelling or pain
- swelling in your legs or feet
- hot flushes
- diarrhea
- vomiting
- cough
- high blood pressure
- shortness of breath
- urinary tract infection
- bruising
- low red blood cells (anemia) and low blood potassium levels
- high blood sugar levels, high blood cholesterol and triglycerides
- certain other abnormal blood tests

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 ZYTIGA. 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 ZYTIGA?

- Store ZYTIGA at room temperature between 68°F to 77°F (20°C to 25°C).

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

General information about ZYTIGA.

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

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

For more information, call Janssen Biotech, Inc. at 1-800-526-7736 (1-800-JANSSEN) or go to www.Zytiga.com.

What are the ingredients of ZYTIGA?

Active ingredient: abiraterone acetate

Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium lauryl sulfate.

Manufactured by: Patheon Inc. Mississauga, Canada
Manufactured for: Janssen Biotech, Inc. Horsham, PA 19044

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: May 2016

051810-160421

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Redwood City, CA 94065
434-220-3774
info@prostatepedia.net
www.prostatepedia.net

Coming Up!

January
Immunotherapy

February
Cardiovascular Disease + Prostate Cancer

March
Using Genomics to Guide Treatment

April
Bone Metastases