Prostatepedia[1]

[1]expert insight + advice

Biochemical Recurrence

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In this issue....

This issue focuses on treatment issues for men with an increasing PSA after prostatectomy or prostate radiation. In this introduction, I will review some basic concepts that should help you follow the discussion more easily.

If surgery has successfully removed the prostate gland, the only source of PSA will be surviving cancer cells. After radiation, there can be normal prostate cells in addition to cancer cells. However, prostate cancer cells differ from normal prostate cells because the cancer cells are able to grow in a particular manner. Cancer cells grow by doubling: 1 cell becomes 2; 2 become 4; 4 become 8. Cancer cells do this at a constant rate.

For example, if the cancer cells double every year, then on subsequent years, the number of cancer cells would be 1, 2, 4, 8, 16, 32, 64, 128, 256, and so on. As a general rule, it takes 15 doublings to go from 1 cancer cell to a mass 1 centimeter across. At 1 centimeter, cancer masses generally become detectable by CT scan. As a rough rule of thumb, it takes another 15 doublings to reach a lethal cancer burden.

The implication is that half of the cancer growth occurs below the level of detectability.

Unlike most cancers, our ability to follow prostate cancer is not limited to imaging tools like the CT or bone scans. We have PSA as a biochemical marker that can be used to follow the cancer. The PSA is a much more sensitive indicator of cancer presence than both CT or bone scan and can indicate the presence of recurrent cancer months to years earlier.

In most patients, the PSA level is roughly proportional to the size of the cancer mass: if the cancer doubles in size, the PSA will double. Thus, the PSA doubling time is thought to provide an estimate of the cancer doubling time. PSA doubling times faster than 3 months usually indicate rapidly growing disease associated with short survival unless treated aggressively. PSA doubling times slower than 9 months usually indicate much less aggressive cancers. PSA doubling times greater than two years are associated with prostate cancers that can take a decade or more to cause metastases detected by the scans.

As a result, it is common to see men after surgery or radiation who have an increasing PSA, but no other evidence of disease. In those patients, PSA doubling time represents the only well established tool to determine the aggressiveness of the cancer and how soon metastatic cancer might manifest itself.

PSA, however, provides no information about the location of the cancer. Is it present in bone, lymph node, liver, or lung?

The recent advances in PET scans mean that the cancer can now be detected while it is much smaller than would be the case with CT or bone scan. However, clinical trials have yet to prove this early detection improves the outcome of treatment.

Finally, there is the problem of late relapses. After surgery, patients can have an undetectable PSA for years—even more than a decade—and then recur. What was going on during that silent interval and what changed to trigger recurrent cancer? This phenomenon is called cancer dormancy and is also reviewed in this issue.

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Dr. Daniel George
PSA Recurrence

Dr. Daniel James George is Professor of Medicine and Professor in Surgery at Duke University.

Prostatepedia spoke with him recently about biochemically recurrent prostate cancer.

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

Dr. Daniel George: As we evolve new therapies and indications for treatment, it's really interesting how that affects our relationships with patients. As an oncologist, my relationships with patients have become more longitudinal. What I mean by that is: people are living longer than ever.

I'm beginning to recognize my treatments in the context of not just the short-term endpoint of how to control my patient's disease in the next few months but in terms of the ramifications for his life and long-term survival. What does it mean in terms of his functional well-being, not simply now, but in a year from now or five to ten years from now?

In many ways, it comforts patients to hear the perspective, that I see them as a long-term survivor, and that I'm thinking about the implications of our treatments in a long-term perspective. That helps the patient invest in his own life and well-being for the long-term, whether that be diet, exercise, sleep, or all these other behavioral interventions that can really impact their quality of life.

You're basically saying that prostate cancer is becoming more of a chronic disease.

Dr. George: It has been for some patients, and we're beginning to recognize it more and more for all patients.

We used to think of short-term goals for some of our most advanced cases of prostate cancer—just in terms of disease control or palliation and not worry about the long-term implications of treatment. While on the other end of the spectrum we would have cases where we don't have to treat the disease at all or maybe treat it minimally in others. Now I'm recognizing prostate cancer as a chronic disease for everybody, and so everybody needs to think of the long-term implications of treatments. Likewise, we need to think of the implications of our sequential therapies and their cumulative side effects.

Can you define M0 prostate cancer, or biochemically recurrent prostate cancer, for patients?

Dr. George: This is probably confusing because of its name. We refer to prostate cancer in terms of stage. Stage refers to the extent of the disease. The Gleason Score or grade refers to how it looks under the microscope, its aggressiveness. But stage refers to the progression of this disease. Do they have bone metastases? Do they have distant lymph node metastases or other sites of disease? Or is it localized?

We usually use three categories: the T stage, which is the localized tumor, the N stage, which is the lymph node status, and then the M stage, which is the presence of metastases that are distant from the prostate. M0 refers to patients who have no distant metastasis. Think of M0 in terms of patients who are newly diagnosed with prostate cancer.

Recurrent prostate cancer patients are those who've had local therapy, surgery, or radiation, and who now have evidence of disease recurrence by PSA. After these treatments, we know that your PSA should be 0 or very low, and it should stay low.

If your PSA rises and continues to rise, that's an indication of disease recurrence. Yet, in many cases, they're what we call M0 because, when we stage the patient with a bone scan or a CT scan, we can't see any evidence of cancer.

Many of those patients have what we might otherwise refer to as microscopic metastatic disease, disease that's just below the level of detection. Some of them could have local recurrence or recurrence just within the pelvis and regional nodes that's not distant. We now know from recent studies that the majority of those patients are going to relapse with distant metastatic disease. In other words, they have distant metastatic disease, but it's just below the level of detection.

So, this is a bit of a misnomer because we're treating them with systemic whole-body treatment therapy now because we recognize the risk of distant metastatic disease for the majority of these patients.

We're beginning to use newer imagining techniques, such as PET scans, that could be more sensitive at picking up this microscopic metastatic disease. That shouldn't deter us from applying the current data to that patient population.

I think of M0 prostate cancer as being low-volume castrate-resistant prostate cancer. When we think of it that way, it makes sense that the drugs we're using work and work even better in that low-volume population. We should use them because M0 is just an early continuation of that metastatic process.

What are these systemic approaches that patients are likely to receive? What are the implications down the line in terms of side effects, and in terms of the longer longitudinal quality of life issues you mentioned earlier?

Dr. George: This is an important aspect of the care for these patients because we have two studies—and a third will soon be reported—that demonstrate a clinical benefit from using what we have broadly termed secondary hormonal therapies, therapies that we add to primary androgen deprivation (ADT) or testosterone suppression.

Patients for whom testosterone suppression has failed can respond to another hormonal intervention later. These are drugs that target the androgen receptor, the protein that testosterone binds to, and inhibits it from signaling. It shuts off what seems to be the most common mechanism for resistance to testicular testosterone suppression. That is an overexpression or overabundance of this receptor, which makes prostate cancer cells sensitive to low levels of residual testosterone in the body.

Xtandi (enzalutamide) and Erleada (apalutamide), in two separate Phase III studies, have demonstrated a clinically significant benefit: a delay in the time to metastasis. The FDA has accepted this as a meaningful endpoint because of the degree of delay. It was associated with about a two-year delay in the time to metastasis in this population.

Patients who were at high risk for developing metastatic disease were in the control arm and developing metastatic disease within about a year of coming on the study for the placebo arm. For the treatment arms, with Xtandi (enzalutamide) or Erleada (apalutamide), we're seeing a delay of about two additional years. That means three years until the time of metastasis.

The results suggest that we've changed the progression of this disease dramatically. In addition, both studies showed a strong trend in favor of the treatment arm for improved overall survival associated with this delay in metastasis.

Even though the data may not be as complete because it takes a longer time to report, we're seeing this correlation in metastasis-free survival, if you will.

Again, I caution the semantics here because these patients do have metastases; they just can't be seen yet. But the delay in that radiographic appearance of metastasis is associated with an improved survival.

What's the approach to finding smaller metastases earlier on with the newer imaging techniques? And if they are very small, do you treat them aggressively with radiation, do you continue using the systemic therapies, or do you use a combination?

Dr. George: There is a mix of presentations of patients. When we image with a novel PET-imaging tracer, we're going to see more than one site of disease in most patients. We're going to see multiple lymph nodes, multiple bone metastases, or maybe lymph and bone metastases.

For a subset of about 20 percent of patients, we see this disease limited to only lymph node disease or only one or two bone metastases. We refer to this as oligometastatic disease, which we have yet to biologically define. Clinically, we know that it's associated with a longer survival.

Oligometastatic prostate cancer raises the question of whether or not these patients could be

managed with therapy localized to those sites, therapy that does not necessarily expose them to further systemic therapy.

We don't have a lot of data in the castrate-resistant setting, but in the hormone-naïve setting, there are some data that suggest that there can be a delay in the time to initiating subsequent hormonal therapy by doing that.

There's a study out of Europe, but the median effect was relatively small, just a few months. It's not clear that this is going to be a meaningful difference for most patients, but it is something that can be discussed.

A lot of those treatment approaches can be done with minimal intervention, external radiation, ablations, or limited surgery. Those will be options. But in the majority of these patients that we do this molecular imagining for, we're going to find evidence of more than one site of disease or multiple lesions. This suggests that they need a systemic therapy approach.

It's reasonable to extrapolate this data because we know from the placebo arm of these studies that these patients went on to develop metastases in their bone scan or CT scan within months, 50 percent of them within a year, and many of them in just a few months of their subsequent scan. The likelihood is, if we'd done the molecular imaging at baseline on these patients, we would have seen it. Yet still, in this population, we're seeing a treatment effect.

We see the treatment effect regardless of what level of PSA doubling time you have. In patients who have a PSA doubling time of just two or three months, we see a dramatic treatment effect. In patients who have a doubling effect of eight or ten months, we still see a dramatic treatment effect in terms of prolongation in the time to metastasis—fewer events in those cases, but still, we see that treatment effect.

The PSA doubling time is an important parameter that we're using now, in addition to these imaging stats, to determine who we should treat with these drugs and their prognosis.

Isn't doubling time an indication of the aggressiveness of the disease?

Dr. George: It is. We knew this earlier in disease prior to hormones. PSA doubling time was very prognostic for time to metastasis and overall survival. It's been less studied in the castrate-resistant setting, when patients have progressed on primary hormonal therapy, but we're still seeing it there. In fact, the results are really dramatic.

There were some abstracts at the Genitourinary Cancer Symposium (GU ASCO) around this data. There have been reports from these two Phase III studies with Xtandi (enzalutamide) and Erleada (apalutamide) that demonstrate this. We believe there is a strong correlation between a shorter PSA doubling time—a shorter time to bone metastasis—and shorter overall survival.

Just to put these studies into context, the requirements were that PSA doubling times were less than ten months. If doubling time is a year or longer, these are slow-growing cancers. Even though they're castrate-resistant, these are patients who will live for many years with no metastasis, so it's reasonable just to observe their disease. For the studies, the median or 50th percentile PSA doubling time was around four months. That's really short and aggressive.

That's why we saw that the average time to metastasis was just about a year in the control arms. It's important to recognize where your patient is in this continuum because it guides whether we should treat him like we did on the study, or if their disease is too slow growing to justify the treatment.

What other considerations are important for patients who fall into this category?

Dr. George: The important thing for patients to know: not to worry. I know that as a physician, it's easy to say 'don't worry about your rising PSA level,' but as a patient, it is hard to ignore. The level's important, but doubling time is your bellweather.

Having a PSA rise from 1.7 to 1.9 might seem worrisome, but the reality is that it's a very small change in terms of doubling, about 10 percent. Depending on the time between those points that can be really assuring for the patient, that they don't necessarily need treatment. Even though there's an indication for it, you can wait on it.

PSA doubling time is not velocity. Velocity is going to rise exponentially. I tell patients, if your PSA doubles from one to two in a year, that's a doubling in one year, but that's a velocity of one point a year. If your PSA goes from 10 to 20 in a year, that's still a one-year doubling time, which is the same prognosis, but that's a velocity now of ten points in a year. That's a much faster velocity. Over time, your velocity will increase, but your doubling time is really what you want to follow.

If patients can keep sense of these two things, it really helps patients make the right decisions because, even though the therapies that we talk about have a high likelihood of delaying the disease progression and suppressing PSA, they come at a cost. And not just a financial cost but quality of life. Therapies can deteriorate a patient's strength, muscle mass, bone density, short-term memory, mood, and balance, while increasing their risk for hypertension, hypercholesterolerolemia, glucose intolerance, risk of falls, and fractures. These complications are mostly reported higher in the study arms than in the control arms of these agents.

It's important for patients to recognize that we don't want to take on those risks unless we need to. For the patients who need treatment, I am happy to do that and help them manage and minimize the risks. For the patients who don't need to do that, it's critically important that we don't treat them sooner than we have to. Those are the two unspoken but important messages that aren't necessarily in the papers, the data, or the labels.

Timing is important here. Not everybody has to be treated immediately. These drugs have long-term consequences that we need to manage.

It goes back to what you were saying in the beginning: some men have prostate cancer for many years, and the treatments that you choose early on can have a profound long-term impact.

Dr. George: That's exactly, right. Even at this stage of disease, as worried as patients may be because their PSA is rising on their ADT, they could still live for a decade or more. Who knows what will happen at that point in time? These are critical insights for patients to have about their own disease status and prognosis in terms of making decisions.

Do you know of any interesting clinical trials that are open and enrolling for men in this space?

Dr. George: The ARAMIS study from Bayer reported at GU ASCO in February 2019. That will be important for patients to look at it because it's a similar drug in a similar disease setting.

These drugs may have differences in terms of their exposure in the body and their side effect profile. That will be important for people to pay attention to.

I suspect there will be follow-up studies with these agents, comparing them in this disease setting. There are not a lot of clinical trials right now in this disease setting because these drugs are relatively new to the market, and they've set such a high bar to beat.

It's nice to know that we've got standard of care options. If you're going to look at anything, maybe non-hormonal therapy strategies, immunotherapy strategies, and vaccine strategies in this disease space might be attractive. Pp

Pedro Barata, MD
What Is Biochemical Recurrence?

Dr. Pedro Barata is an Assistant Professor of Medicine at the Tulane Cancer Center. He's keenly interested in genitourinary tumors with a particular focus on clinical trials.

Prostatepedia spoke with him recently about biochemically recurrent prostate cancer.

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

Dr. Barata: As a genitourinary-focused medical oncologist, mainly I treat patients with prostate cancer, kidney cancer, and bladder cancer. Over the years, I try to remember most of my patients, but usually striking stories with outcomes that you're not expecting are the ones that you start wondering about. Why didn't things go the way they were supposed to go?

I'm thinking in particular now of a patient with very advanced prostate cancer. We treated him with a number of different treatments, and unfortunately, his tumor was very aggressive, didn't respond well at all to those treatments, and progressed.

As an act of desperation, we were able to offer him immunotherapy. He remained on immunotherapy for a long time, more than a year; that was totally unexpected. We thought we'd try this immunotherapy and see how it goes. We didn't have a good biomarker to predict response to that treatment, but the reality is that this patient responded for over a year, continued his life, and continued to do things.

This is just one example. I have more of those similar stories where the standard of care treatment available fails, and then we are able, for one reason or another, to offer a treatment for which there's not a lot of data or that is still in clinical development, and you see these amazing responses.

It's a good reminder that we don't know everything and that there is a lot for us to discover and to learn. Also, sometimes our predictions don't really matter. We might predict a response to how well a patient's going to do on the treatment, but sometimes we are wrong and cannot anticipate what's going to happen.

We need to keep trying, keep doing research and testing novel medications, and keep asking smart questions in a proper manner because these are the only ways we can improve the outcomes of these patients. Sometimes great responses to treatment happen, and that makes a dramatic change in their lives.

What is biochemical recurrence?

Dr. Barata: When someone has low-risk prostate cancer, there is data showing that active surveillance is a valid option. In men with intermediate-risk or high-risk prostate cancer, there are definitive treatments, which can include surgery or radiation, with or without hormonal treatment. The goal is to treat the patient, and hopefully, the patient will be cured, meaning he will have no evidence of disease afterwards. However, disease might come back later on.

Biochemical recurrence is a consequence of us using a biomarker, such as PSA, to predict recurrent disease, meaning disease that returns after an interval free of disease.

Biochemical recurrence is a serologic recurrence, a disease that comes back after definitive treatment, but it is defined depending on the prior treatment that you got for prostate cancer.

For instance, if you had surgery where you basically removed the prostate gland and you also removed the lymph nodes for prostate cancer, your PSA after surgery is usually undetectable, so zero. Biochemical recurrence in those cases is defined by a repeated detectable PSA that reaches 0.2 or above.

However, if a patient received radiation therapy plus or minus some form of hormones for a short or a longer period of time, then the biochemical recurrence is the nadir, meaning the lowest PSA number after the treatment with radiation + hormones plus two. Why plus two? Because for patients treated with radiation + hormones, we allow some detectable PSA, and so we add two to the lowest PSA value after that treatment.

Is that because the goal with radiation therapy isn't to totally remove the prostate, or is it because there's something about radiation therapy that impacts the PSA reading itself?

Dr. Barata: Only the prostate produces PSA and nothing else in the body. So unless you leave behind a little bit of prostate tissue or prostate cancer when you remove the prostate gland, your PSA will be zero because you don't have more prostate gland producing PSA.

If you get treatment with radiation + hormones, you actually kill prostate cells that replicate. It's possible that you don't kill 100 percent of the prostate gland or the main tumor. Radiation normally has similar outcomes to surgery. It's possible that some normal prostate cells remain alive, and so it is possible that you still produce a little bit of PSA. It's possible to have a detectable PSA after radiation therapy.

What are some of the key issues when it comes to how we approach men with biochemical recurrence?

Dr. Barata: It depends on when biochemical recurrence happens because it can happen soon after the definitive treatment.

It also depends on the treatment that you got to treat your prostate cancer. If you had surgery in the past and now have biochemical recurrence, we might think about other treatment options such as radiation, plus or minus hormonal therapy. However, if you got radiation therapy in the past, we usually don't re-radiate the tissues because there's a limit on the radiation that you can deliver to a patient without compromising safety.

"There is a lot for us to discover and to learn."

The absolute value and doubling time of your PSA also matters, meaning that it's different if you have a rapidly rising PSA versus a PSA that takes a year or two to double. When we have someone with biochemical recurrence, we consider whether we can offer the patient salvage treatment and still try to cure him, especially if he had a radical prostatectomy.

Let's assume for a second that a patient developed recurrent disease and got radiation in the past. It's a waiting game until you have a higher PSA number. That's when we consider how to scan him and repeat scans to see if we can detect metastatic disease because that will direct the way we're going to treat him.

After salvage radiation, with or without hormones, the same thing happens. If the PSA begins or continues to rise afterwards, then the next question is: when is a good time for us to actually scan these patients and define what are we going to do next? This impacts the way we treat the patient and whether we see metastatic disease or not.

The type of scans we use also matters. We can use conventional scans, including CAT scan and bone scan, or we can use fancier scans called PET scans.

Can you talk a bit about the PET scans?

Dr. Barata: We know that in the context of a rising PSA and a biochemical recurrence for low values of PSA, conventional scans are not good. There's a chance that they will miss very small metastases called micrometastatic disease because the CAT and bone scans are not perfect.

The newer PET scans are more sensitive to pick up disease. They are like CAT scans, but you inject a different, prostate-specific tracer. That gives you functional data as well as anatomic data.

There are different tracers out there. Probably the two best tracers are PSMA, which is not FDA approved, but we had recent data suggesting that it's probably the most sensitive PET scan available. Fluciclovine PET scan seems to be the second best. Then you have choline PET, but recent data also shows that fluciclovine PET is better than choline, and PSMA is the best. It's a changing field where we

"The newer PET scans are more sensitive."

now have a PET scan that is FDA approved, and we have interesting data with another PET scan that might be approved in the near future.

Using those scans allows us to detect disease sooner and has potential therapeutic implications.

What is NRG Oncology?

Dr. Barata: NRG Oncology is a non-profit research organization of research physicians. We meet together with the goal of conducting clinical research and clinical trials in oncology that will answer important questions in the field.

NRG is the product of the National Surgical Adjuvant Breast and Bowel Project (NSABP), the Radiation Therapy Oncology Group (RTOG), and the Gynecologic Oncology Group (GOG). These three cooperative groups merged into NRG Oncology.

In NRG Oncology, there are subcommittees according to the type of disease. You have a genitourinary (GU) committee formed by a group of research physicians, and then you have the same for gynecologic malignancies, for breast malignancies, etc. It's a group of physicians and researchers who investigate and conduct research in those areas, and this usually includes medical oncology and radiation oncology.

It's an opportunity for us to use radiation and medical oncology to help design good studies that will give us good data and change the way we practice medicine to improve patient care.

Do the clinical trials that NRG Oncology coordinates tend to be larger-scale?

Dr. Barata: Yes, that's one of the benefits. Let's say that your research investigator wants to start a study in his own academic institution. The ability to conduct that study is relatively limited because of resources, scale, the number of patients, etc. Single institution studies are usually small proof-of-concept studies.

To answer a definitive question, sometimes you need a very large number of patients to be involved in that study, which is one of the benefits of a large study.

You do it in either one of two ways. One, you have pharmaceutical companies that, for some reason, have their own interests and their own therapies and test them by funding and sponsoring the study. Or two, you have cooperative, academic groups that have no pharmacological company biases. Sometimes they might have indirect support, meaning the question to be answered has nothing to do with the pharmaceutical company's interests, only the academic interests of answering questions to help patients.

Cooperative groups have the ability to conduct larger studies. Hundreds and sometimes thousands of patients are involved in a single study, and then we'll have an answer that will translate into a meaningful, clinical change to patient care.

Are there any clinical trials currently being run within NRG that focus on biochemical recurrence?

Dr. Barata: Yes, there is a Phase II placebo-controlled trial being conducted by the NRG called NRG-GU006. They are randomizing patients to salvage radiation therapy, with or without an anti-androgen therapy with Erleada (apalutamide), which is a very effective antiandrogen. Erleada (apalutamide) is already approved in prostate cancer in the nonmetastatic castrate-resistant setting. And it's already approved later on, but we don't know whether the addition of these molecules to salvage radiation improves outcomes of these patients, and so that study is trying to answer that question. It's not open to Academic and Community Cancer Research United (ACCRU), but it will be soon.

We have two more studies being designed by NRG that aim to answer the question of whether genetic data play a role in treatment selection in patients with biochemical recurrence. Also, we're looking to answer whether there is a role for treatment intensification or treatment deintensification based on the tumor's clinical and genomic characteristics.

These studies will be open soon, and we'll be able to enroll patients in those studies.

If there are men reading this who want to learn about the trials once they're open, should they contact you directly or is there somebody at NRG that they can contact to get on a waiting list?

Dr. Barata: All of the above. Every time we have a trial available, I'm more than happy to see those patients and talk about these studies or others that we might have available at each given time. If we don't have a study available for that patient,

"Cooperative groups have the ability to conduct larger studies."

or let's say the patient lives far away, and we happen to have site that's closer to home, we can refer that patient to another center where he can be treated on the same study.

I'm open to see any patient who's being considered for a study or even has a question about the management of his disease. Then we can help patients identify the best sites for them. Not everybody lives in New Orleans or Louisiana, and not everybody can fly out of state to see us, so we help them to identify the best option for them. If the best option is indeed the clinical trial, we can help them identify the closest site where the same study is being offered, and they can actually participate if they are interested.

Any advice for men who've been told they've got biochemical recurrence? Do you have any thoughts that they might want to keep in mind as they approach treatment?

Dr. Barata: We usually say to patients that it's important to get the thoughts of a team who works in a multidisciplinary manner. It's helpful when medical oncology works together with urologists and radiation oncology. Oftentimes, I see patients who, for some reason or another, were not offered the opportunity for radiation therapy, they didn't discuss hormonal therapy, or they didn't discuss new imaging because they kept with their local team and were not aware of those options.

I recommend second opinions. I tell my own patients that I'm more than happy to recommend a different team just so that they have a sense of what to do. People in the community, we're happy to see those patients and help the local team to discuss those options. At the end of the day, if you know the options and you make a decision, you are making the decision in an informed manner. Hopefully that will impact the way we treat patients.

My advice is to search for multi-disciplinary teams such as our team at Tulane, obviously, but also other teams around the country, where the different urology, medical oncology, and radiation oncology teams work together. When they work together—and we have clear data showing this—patients are aware that they have options.

This is the case at Tulane, where we are launching a multidisciplinary clinic where medical oncology, urologists, and a radiation oncologist will all see the patient at the same time. We are taking patients within two or three days of their first contact. We go over the scans, the pathology, and the clinical information with them, and we all see them at the same time. Based on that, we will recommend the best course of action for that patient as a team. Pp[1]

For more information …

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Julio A. Aguirre-Ghiso, PhD

Predicting Cancer Dormancy + Recurrence

Dr. Julio Aguirre Ghiso is a Professor of Medicine, Hematology and Medical Oncology and Oncological Sciences at Ichan School of Medicine at Mount Sinai in New York City. His research explores why and how in some patients disseminated tumor cells can remain dormant for years after initial treatment before reactivating to form incurable metastases.

Prostatepedia spoke with him about his research and about a clinical trial testing his findings that is currently looking for prostate cancer patients.

Why did you become involved in cancer research? What is it about cancer research that has kept you interested?

Dr. Julio Aguirre-Ghiso: When I was an undergraduate student, I was looking for challenging problems to solve in biology. Serendipitously, I started working and volunteering for a cancer biology team in Argentina, where I trained. I became very interested. I was working on tumor immunology. Then I became very interested in the cell biology of cancer cells. At some point, I realized that it didn't really matter if it was cancer or Alzheimer's or some other basic biological questions on other organisms; what I really was curious about was solving tough problems and answering questions. This was a good mix where, if I were able to do it, I would also be helping people with cancer in the future.

Focusing on cancer would give me an opportunity to apply my curiosity to something that is relevant for people. That was the original intention. Since I was not an MD, my curiosity was about mostly biological questions. This was a fitting problem to go after.

That's why you originally became interested, but what has kept you there?

Dr. Aguirre-Ghiso: My research program has evolved into both a basic science and translational program, where we ask basic science questions, or basic mechanism questions, about how cancer functions. We bring them to a practical reduction in patients, or we bring our findings to industries for further development to bring them to patients. That initial curiosity about understanding mechanisms is still there because we still ask very basic questions about why cancer cells do certain things and how can we understand and take advantage of them. That part is still there; it keeps feeding my curiosity.

Obviously, that has evolved now in a way that we can now take that information and bring them to industry; they can use that information to generate antibodies or drugs. Also, we can apply it to patients by, for example, repurposing drugs. It's obviously matured a lot more and it's a lot more focused, but I think the original intention of understanding biological problems and solving them is still there.

Let's talk about the concept of disseminated tumor cells. Can you explain to us how that works and how it is related to the development of metastasis?

Dr. Aguirre-Ghiso: Patients usually present with what's called a primary tumor. That's the first cancer lesion ever found in that patient. At that time, doctors will do certain tests on that primary tumor to understand if it had gone through certain changes that would make it able to spread. When cancer cells grow, they may acquire certain abilities that allow them to spread from that primary site—from, let's say, the prostrate or the breast—to other parts of the body.

The disseminated tumor cells are these cells that have spread throughout the body. They have disseminated from the primary tumor to other organs in the body. Those could be the bones; the liver; the brain; or the lung. When they arrive to those organs, they're not immediately able to grow. Since they're usually solitary cells–that's how we find them in the patient samples and in the mouse models that we've used—we call them disseminated tumor cells. They're not yet metastases, but they're not in the primary tumor. They've left and arrived to other organs. That's the definition of these disseminated tumor cells.

Why are they important? We and others have provided compelling evidence that these cells are the source of the metastases. Those are the cells, not all of them, but some of them, that are able to eventually grow into metastases that affect the functioning of the organ, and sometimes systemically, the functioning of the patient. That's what leads to death. That's why these cells are important.

Do all disseminated tumor cells eventually grow into metastases?

Dr. Aguirre-Ghiso: No.

How do you know which disseminated tumor cells are going to grow into metastases and which are not?

Dr. Aguirre-Ghiso: Well, that's been a major challenge and a major push from my program: to try to get in early and identify those disseminated tumor cells so that we have some idea if a patient carries disseminated tumor cells that are not going to do anything and the patient doesn't have to worry, or if the patient carries some cells that look like they're switching and they're going to form metastases.

That has been our goal. It's not yet a clinical test, but that's why we have pushed the boundaries of our research to get to that point as fast as possible because we think that instead of waiting and not doing anything or treating blindly and then waiting until those metastases grow, we can intervene earlier. We would like to be able to say that this patient has only dormant cells and they don't look like they're going to reactivate based on certain markers or gene signatures. That patient would then only need to be monitored, but new treatments may allow eliminating even those cells. If another patient has a mixture of cells some of which are fully dormant and some of which look like proliferative cells, we would treat him in a different way.

We have provided data for this from our mouse models and from clinical patient samples in prostate cancer. We published two papers in 2014 and in 2015 on this.

Not all cells are going to grow. In fact, if you look at early lesions in breast cancer, for example, disseminated tumor cells are found in the bone marrow of 13-15% of women with ductal carcinoma in situ but only a small fraction of that 13-15% will develop metastases.

It's not a given that if these cells are there they're going to grow, but if they are there, there is a higher risk of metastases. That has been proven by large population studies that have been published in *The New England Journal of Medicine*. This is true for not only breast cancer but for other cancers as well. The goal and the challenge is to have enough information to be able to predict accurately what those cells are going to do when you detect them.

Where we are in the timeline of being able to predict which patient is carrying potentially dangerous disseminated cancer cells and which is carrying dormant disseminated cancer cells?

Dr. Aguirre-Ghiso: We have different areas of research into these disseminated tumor cells. Why they are dormant? Why do they sleep in the body for a long time and then awaken? We discovered a marker in 2015 that could distinguish these deep-sleeping cells in both prostate cancer and breast cancer models. If the cells had this marker, they would behave in this dormant way, and if they didn't have this marker, they would look more like a proliferative or an about-to-reactivate cancer cell.

At that time, it was correlative between just two groups of patients. Last year, we published a paper on breast cancer where we used the same marker detected in tumor cells disseminated to the bone marrow of breast cancer patients. We were able to show that if patients had this marker they were much less likely to relapse with bone metastases than if they didn't have this marker.

In 2015, we've published the original finding where we just said this is probably a good marker; we understand how it works in mouse models. In 2018, we showed that the presence of the markers can distinguish retrospectively how patients behaved. Now the challenge is for people to start using the markers prospectively to see if it helps them make decisions on how to treat or monitor patients.

We are very much at the early stages of applying the information that we

have generated and bringing it into the clinic.

On the other hand, in that same 2015 paper, we were able to show that if we use two drugs that are FDA-approved and combine them in sequence, we can turn on these dormancy mechanisms in different types of cancer cells—i.e. breast, prostate, and head and neck cancer cells. Because these drugs were available—and there are independent studies showing that when prostate cancer patients are treated with hormonal therapy and anti-androgens, they turn on this marker of dormancy that tells you the cancer is deciding to go into sleeping mode—we wondered if we could repurpose those drugs and treat prostate cancer patients at risk of developing metastases to see if we could delay the onset of metastasis and keep the disseminated tumor cells in a dormant state.

That work is funded by the V-Foundation and our Tisch Cancer Institute at Mount Sinai. We have an active clinical trial where we are monitoring how this therapy functions in prostate cancer patients. That's another example how we were able to bring, within four years, something from basic science to the clinic. [For more information about this trial, visit https://clinicaltrials.gov/ct2/show/NCT03572387].

What are the two drugs that you're using in the trial??

Dr. Aguirre-Ghiso: Vidaza (azacitidine) followed by retinoic acid.

So that is one instance in which you're taking the information you've learned in the lab into the clinic to see if there is any direct application.

Dr. Aguirre-Ghiso: Right, so those are two examples in breast and prostate cancers. It takes years to get these things done, so we are slowly testing some of the other markers. I know other groups have picked up on our research and are testing one of the markers we discovered in colorectal cancer and liver metastasis. Others have been looking at how the immune system, or cytokines involved in the immune system, is turning on these in melanoma. It's the nature of research. You put the information out there, you do the best you can to validate it and help it move forward, but the data has a life of its own and other people have to help expand it.

The other thing that we've done to bring our science to patients faster is create a company to capitalize on all the knowledge-base that we have generated in the lab about dormancy, metastasis, and disseminator cell biology. We identified certain drugs that can kill these dormant cells and we identified certain drugs that can keep them in that sleeping mode. The company, HiberCell, is now moving forward to bring those drugs into clinical trials

Is there any way for patients or the doctors to use the information you've already identified to force their cancers into a state of dormancy?

Dr. Aguirre-Ghiso: As far as I know, ours is the only trial that is available for inducing or maintaining dormancy in prostate cancer.

A lot of people are working on trying to prevent metastasis by understanding the biology of disseminated tumor cells. It's important to support that research because it could be a game-changer for patient outcomes. Pp

Rahul Aggarwal, MD
High Risk Biochemically Recurrent Cancer

Dr. Rahul Aggarwal is an Associate Clinical Professor of Medicine in the University of California, San Francisco Genitourinary Oncology and Developmental Therapeutics programs. He's keenly interested in developing novel therapeutics and imaging strategies for men with advanced prostate cancer. Dr. Aggarwal is a Co-Investigator in the ongoing Prostate Cancer Foundation's Stand Up To Cancer-funded West Coast Dream Team prostate cancer consortium.

Prostatepedia spoke with him about his clinical trial on hormonal annihilation in men with high-risk biochemically recurrent prostate cancer.

Why did you become a doctor? What is it about medicine that's kept you interested?

Dr. Rahul Aggarwal: I became a doctor because I think it's a really fantastic blend between patient care and science. I like having the ability to take care of patients, yet still keep scientifically engaged. That's what keeps it interesting. In particular, oncology is at that intersection between patient care and science. I have a science background and have a lot of scientists in my family. At an early age, I became interested in science and math and wanted to learn and discover, but the patient care piece was really central. Patient care is what keeps me motivated on a day-to-day basis. Even if there are frustrations, as we all have from time to time, on the research side of things, it's still incredibly rewarding to take care of patients with cancer day in and day out.

"Patient care is what keeps me motivated on a day-to-day basis."

What is the thinking behind your clinical trial on hormonal annihilation in men with high-risk biochemically recurrent prostate cancer?

Dr. Aggarwal: This trial is for patients with prostate cancer who previously had what we call a radical prostatectomy, or the prostate was removed, as their primary treatment and then subsequently had evidence of cancer recurrence as indicated by a rising PSA. We're specifically looking at patients with a PSA that is rising quickly with a PSA doubling time of nine months or less.

We know that this group of patients is at risk for subsequent development of metastases as well as at risk for prostate cancer-related mortality.

One standard treatment approach is to use intermittent hormone therapy, which can suppress the cancer for a period of time. Inevitably, though, the cancer becomes hormone or castration-resistant. Once that happens, patients have fewer treatment options remaining and a shorter prognosis.

The main goal of the study is to use some of the more potent hormonal therapies that have been developed, including Zytiga (abiraterone) and Erleada (apalutamide). and apply them to this situation to see if we can durably suppress the patients' prostate cancer in a finite period of treatment. Rather than treating indefinitely, we treat everyone on the study for 12 months, and then we stop and let their testosterone levels recover and any side effects related to hormone therapy stop or lessen. Hopefully, we can see long-term control of patients' PSA levels or maybe for some prevent the need for future treatment.

In this way you would also lessen some of the side effects associated with these treatments?

Dr. Aggarwal: Exactly. Then the total duration, or percent time, spent on hormone therapy would be shorter. Even though we're giving more potent hormone therapy, this would actually translate into less overall treatment and less medical burden from a side effect perspective. Some of the other studies that have come out using medicines like Zytiga (abiraterone) and Erleada (apalutamide) in the hormone sensitive or castration resistant settings do seem to suggest there is a benefit to giving these medicines earlier in the treatment course. I think it fits with what we're seeing in terms of the general trends in the use of these medicines and the management of prostate cancer.

What can a patient expect to happen step by step if he ends up participating?

Dr. Aggarwal: The treatment phase of the study consists of monthly visits for a year in which patients are getting hormone injections. Then it is a randomized study, so in the standard of care arm men would be getting the hormone injections alone once a month for a year. Then there are two experimental, or investigational, arms with added hormonal therapy. One arm has added Erleada (apalutamide). The third arm adds Erleada (apalutimide) plus Zytiga (abiraterone).

Patients have a two in three chance of being on one of the added hormonal treatment arms.

This is an open label trial, meaning there is no placebo. Everyone will get active treatment, so there's no risk that their PSA levels won't go down. Every patient responds initially to hormone therapy, or nearly everyone. We see patients monthly for hormone treatments. We evaluate them for side effects.

At four or five time points throughout the study, we have patients fill out questionnaires regarding their symptoms. We do want to understand from a patient perspective what quality of life and symptoms are like during the course of treatment.

After one year of treatment, assuming the PSA is not rising, patients will then enter a follow-up phase which we try to make easy. We check patients' PSA and testosterone levels once a month, but we don't require any mandated in-person visits to allow more flexibility for those who live far away from the study center where they were treated.

At the time that the PSA rises to above 0.2, that's the cut off for what we call PSA progression, which is the primary endpoint of the study. After that treatment is per the discretion of the patient and treating doctor. We still follow patients long term for metastases-free and overall survival. The treatment options at that point are completely up to whatever is decided upon between the patient and his doctor. It's flexible on the backend too if his PSA were to rise.

Are there any specific eligibility criteria that you'd like to highlight?

Dr. Aggarwal: These patients have to have had prior radical prostatectomy for treatment of prostate cancer. They may or may not have had prior salvage radiation. (That's allowed but not required.) Their PSA has to be rising with a doubling time of less than or equal to nine months. They cannot have evidence of cancer spread on standard imaging, meaning a whole body bone scan and a CT or MRI of the abdomen and pelvis.

"Rather than treating indefinitely, we treat everyone on the study for 12 months."

Do you have multiple study locations?

Dr. Aggarwal: There are over 50 sites open across the United States. This is an Alliance Foundation Trial, so we use the Alliance Cooperative Group network. All the sites are Alliance members or affiliate members. We currently have 54 or 55 sites across the US. There's very likely to be a site not too far away from most patients.

But for follow up patients don't have to visit a site?

Dr. Aggarwal: There still would be telephone contact and electronic contact with the study site, but in-person visits are not mandated during that period of time.

Are there any fees associated with the trial?

Dr. Aggarwal: The hormone injections are considered standard of care, so that would go through patients' insurance, as are some of the routine lab monitoring,

For more information…

Contact Dr. Rahul Aggarwal at Rahul.Aggarwal@ucsf.edu or the study administrator at AFT19@alliancefoundationtrials.org.

things like checking the patients PSA. That's considered standard of care in this setting. The Zytiga (abiraterone) and Erleada (apalutamide) are definitely provided by the study, so those are not sent to patients' insurance. Generally, it is pretty straightforward in terms of study cost: nothing more than what is considered standard of care.

"This group of patients is at risk for subsequent development of metastases as well as at risk for prostate cancer-related mortality."

Is there anything else you want patients to know either about this trial in particular or the context in which it's occurring?

Dr. Aggarwal: The overall intent is that this changes standard of care for patients with a rising PSA and durably improves treatment outcomes for patients with this type of recurrence. We're excited about the study. It's accruing quite well across all sites, but there are still plenty of opportunities to participate if patients are interested. Pp

Clinical Trial: Gay Men + Prostate Cancer

Mr. Darryl Mitteldorf, an oncology social worker, is the founder of Malecare.

Prostatepedia spoke with him about a clinical trial Malecare is running for gay men with prostate cancer.

How did you get involved in prostate cancer advocacy and with Malecare?

Mr. Darryl Mitteldorf: I've been a social worker for almost 27 years. I was working in Europe and Africa doing refugee settlement social work when my dad was diagnosed with prostate cancer, 21 years ago. I came back to New York City to help him and my mom with caregiving. When I arrived, I thought he was going to be dead in two months. As we all know, you can live many years, as he did before passing from prostate cancer.

I could see he was eager to meet up and talk with other men, but the support groups that existed in New York during the late 1990s were just lectures and marketing events masquerading as support groups. With a lot of time on my hands, I started a real psychosocial peer-to-peer prostate cancer group.

As part of a newly emerging field of psycho-oncology, which was just getting revved up at that time, it became an overwhelming success. We were having 12 meetings a month, 2 to 3 per week in lower Manhattan.

The Malecare psychosocial model seemed to be helpful for a lot of guys. Many psychologists and social workers in other cities heard about it and wanted to replicate it. We formed a nonprofit just to have a structure to spread this kind of modality around the country: Malecare was born. Since about 2005, we've developed over 100 different support groups in the United States.

Then the Malecare style of prostate cancer support groups started spreading throughout Europe and countries like Australia, South Africa, and more. We started an organization called the Global Prostate Cancer Alliance to help disseminate the style of doing psychosocial support for prostate cancer as well as to share cross-border information and advocacy.

Along with that work, we identified several underserved communities such as African-American men, gay men, Native American men, undocumented workers in Germany, and Brazilian men: all presenting with an extraordinarily different psychosocial need-set.

My interest regarding how prostate cancer affects gay men was critical to developing the field of LGBT psycho-oncology, for which I'm considered a pioneer. In 1998, we started the world's first gay men and prostate cancer support group. And in 2005, we started the National LGBT Cancer Project, the world's first support and advocacy nonprofit for Lesbian, Gay, Bisexual and Transgender people diagnosed with cancer.

"Since about 2005, we've developed over 100 different support groups in the United States."

Because of Malecare and our collaborations with brilliant community-based patient advocates, almost every continent now has a support group for gay men with prostate cancer, from South Africa to Iceland, from the United States to Australia. We've done a lot of work that's helped many men, their families, and caregivers.

This year we're going to see 50,000 active men and family members who participate in our services. We thought accrual was such a critical issue around clinical trials and research, so we looked at how we could invest in the larger research community with an ease of recruitment. We've been very successful with that.

We've saved months and years of work for several trials and research projects in the United States and Canada. Malecare has also developed several small-scale research projects of our own, including one this year that we're collaborating with the University of Minnesota on. It's a fully funded, multi-million-dollar NIH-funded clinical trial on urinary and sexual rehabilitation of post-treatment prostate cancer patients. We're certainly one of the very few patient advocacy nonprofits that has an NIH-funded clinical trials under our wings.

What is the thinking behind this trial?

Mr. Mitteldorf: Doctors typically offer treatments that are based on evidence. Evidence comes from clinical trials, studies of how men react to different kinds of treatments. Most people are familiar with Phase I, II, and III trials. A doctor would be loath to suggest a treatment that wasn't based on that kind of evidence.

Unfortunately, around physical rehabilitation after initial prostate cancer treatment, which refers to impotence and urinary incontinence for the most part, all the trials that have been conducted have focused on heterosexual men. Doctors do not truly know how to treat a gay man or a man who enjoys sex with men for urinary incontinence or impotence because there's no evidence-based protocols for them.

For more information …

About participating in our clinical trial visit:
www.malecare.org/restore

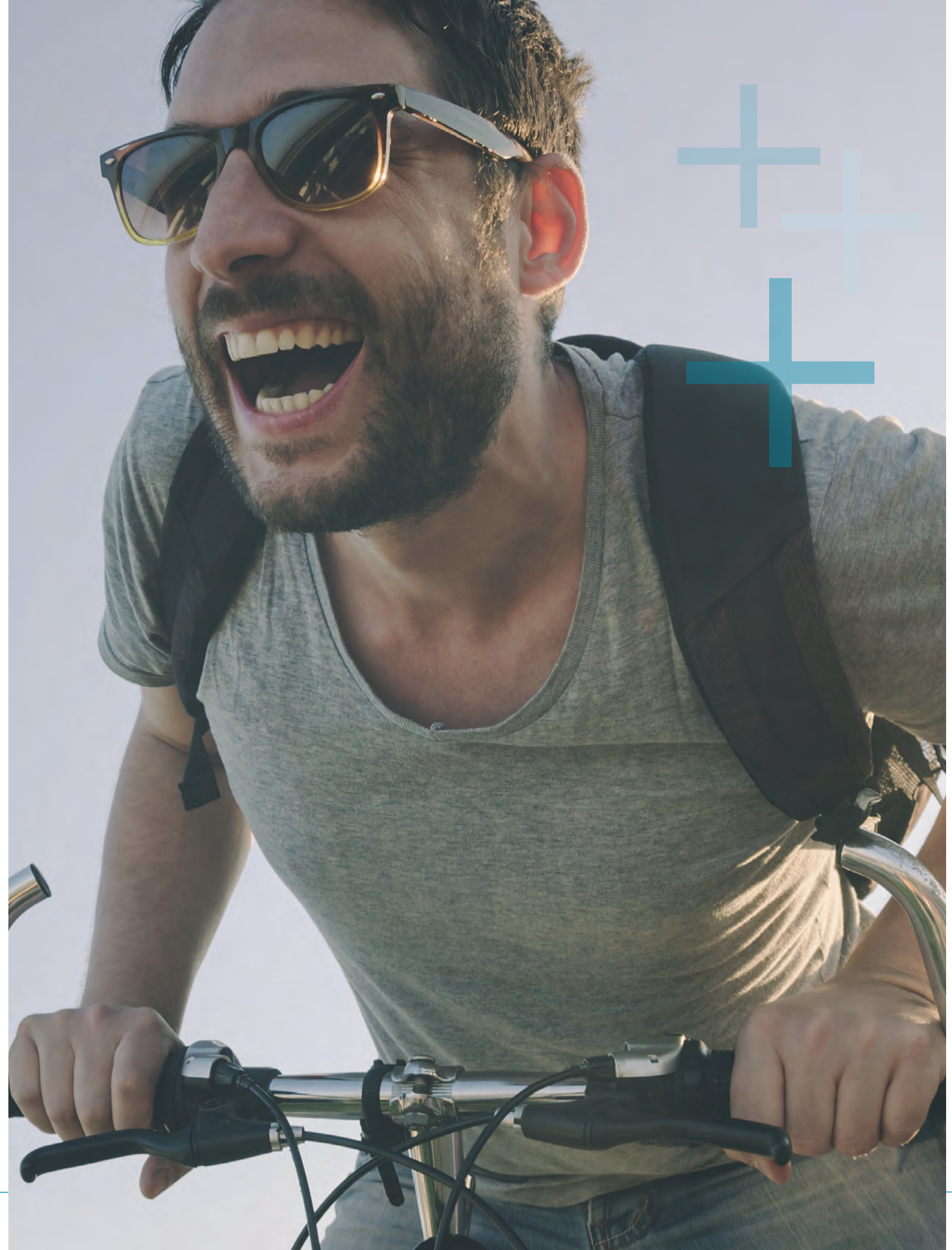
We have designed an evidence-based study in a classic, randomized control trial setting that will demonstrate whether or not a structured rehabilitation program focused for gay men with prostate cancer will be more effective than routine care, which is currently based on straight men with prostate cancer.

"All the trials that have been conducted have focused on heterosexual men."

Walk us through what patients can expect to happen if they end up participating.

Mr. Mitteldorf: The rehabilitation modality that we're testing out for men who were treated involves medication and appliances like vacuum pumps. Some men will be coached via Skype. We'll be testing different videos and different ways to approach men around helping them regain pelvic floor control and erectile functioning to reinvest happiness into their lives. Basically, we're investigating which types of treatment doctors might offer a man who enjoys sex with other men that is specific to them, that can restore the happiness that they had before their treatment for prostate cancer?

It's a 24-month trial. People who enter it will be expected to hang out with us for two years. It doesn't prevent them from doing other kinds of treatments. They are welcome and encouraged to do other kinds of treatments. We're doing it in conjunction with their doctors, and everything's paid for as well. In fact, we're going to give $200 to each of the participants as a thank you at the end of their participation.



Who is eligible for the trial?

Mr. Mitteldorf: It's open only to residents of the United States who are gay or bisexual by their own identification and men who tell us that they have sex with other men. Men on the down low, who are quiet about it, don't have to be identified as gay or bisexual, but they must have sex with other men.

They have to have been treated for prostate cancer–anytime in the past–with any of the initial treatments, typically radiation, high intensity focused ultrasound (HIFU), and surgery.

Finally, they have to have difficulty with urinary and/or sexual functioning.

What else should patients know either about this trial or others that you may be running?

Darryl Mitteldorf: The context for this trial elevates the idea that gay men with prostate cancer have unique needs, not only psychological, not only social, but physical needs.

Malecare did a study during 2015 and 2016 that showed that gay men have a more favorable long term presentation of prostate cancer than straight men. We looked at a group of gay men and a group of straight men in a retrospective study that showed that gay men are less likely to navigate into an advanced stage of prostate cancer treatment and less likely to have recurrence of their cancer than straight men. No one knows why. There's a whole world of investigation yet to be completed around that.

The context of the study is actually LGBT civil rights, LGBT health, LGBT awareness for our community, and in an even larger sense the idea that heteronormative white studies don't necessarily apply to gay men, African-American men, Asian men, and Native American men. Everyone presents with a unique cancer profile. In our "age of precision medicine," who a person is matters as much as their biology. One man, one tailored treatment.

"It's a 24-month trial."

Investigations that focus on unique cohorts of people lead to greater understanding of what are the better treatments for all of us. It's a way to arm doctors with better ways to treat their patients as individuals, precise treatments based on who the man truly is. Malecare is about empowering patients. And, we are now embarking on a process that empowers patients to seek individualized treatments. Malecare hopes other nonprofits follow our leadership in creating innovative projects and collaborations with academic institutions towards improving patient care.

When you understand people with specific differences, you can create an approach to treatment which is adaptable for people with all differences. That's essential. Po!

I'm Hiding From Prostate Cancer by Dave Fuehrer

Dave Fuehrer is the CEO of GRYT Health, creator of Stupid Cancer, the most used app in all of oncology.

Dave writes about confronting prostate cancer within his own family.

I'm a two-time cancer survivor and I work in oncology.

I wake up every day to use my survivor heart and my researcher brain to improve the treatment, care, and quality of life for families facing cancer.

My family is facing metastatic prostate cancer now and I'm paralyzed. The fact that I've gone through cancer twice myself and work in the field makes me think I should know how to handle cancer. But when it's happening to my family, it's different.

This feeling is exactly how I felt going through my own diagnoses.

I shut down.

I shut it out.

My family had no idea what I was experiencing because I couldn't let them in.

I think this is especially true for men. When I was going through cancer, I told myself I didn't want to burden my family. So, I didn't say anything. With 10 years of self-reflection under my belt and working in the cancer community, what I've come to realize is that I couldn't ask for help because I couldn't admit to myself that I needed help.

"I'm supposed to be strong. I'm supposed to take care of my family. I'm supposed to provide."

These are the thoughts, conscious and subconscious, that overwhelmed my brain during my diagnoses. I couldn't admit that I was the one who needed help.

In the years since, I've found a place of acceptance. I'm learning to accept myself. And I'm finding ways to talk about it. Some topics are still much harder than others.

We have a family party tomorrow. It's the birthday of our loved one with metastatic prostate cancer. I'm going to ask how I can help him. I'm going to ask his caregiver how I can help her. I'm going to ask. For them and for me.

I thought working in the cancer community for nearly a decade had helped me learn how to face anything cancer throws at us. I'm learning however, there is still much more I have to learn.

If I've discovered any one constant in living a life facing cancer it's that I can't face it alone. I need the support of others. I need a way to learn what I don't know. I'm learning how to ask.

If you want to find resources or ways you can help, here are a few that I and our team at GRYT Health provide:

For Patients and Families:

If you are going through a prostate cancer diagnosis, or someone you love is, download the free GRYT Health Cancer Community app from the Apple App Store or Google Play Store (download links to both are here listed to the right). It's a safe, anonymous place to find support, connect with others, and learn what you didn't know you needed to ask.

For Those Wanting To Improve The Patient Experience:

You can also check out The GRYT Project. It is a place people can sign up to have your voice heard about topics that could help shape the future for healthcare. As we become involved in future studies, we ask our app users and those who are a part of The GRYT Project to lend their unique experience and voice.

For Advocates and Support Providers:

If you lead support groups or provide resources, contact us. We'd love to let others and their families know about you. We'd welcome the opportunity for you to lead a live, in-app program, (we call these AppChats!) for patients and caregivers around the world to learn about you, your organization, and a beneficial topic for the cancer community. You can find contact information for Aerial, our Programs Director, on the program page that we've listed below.

Anyone can learn more and connect with the GRYT community at:

- Our website: https://grythealth.com
- Our blog where we post GRYT profiles, AppChat recaps, and more: https://medium.com/the-gryt-blog
- Facebook: https://www.facebook.com/grythealth/
- Twitter: https://twitter.com/GrytHealth

Join the conversation. I hope to see you there. Pp[1]

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Coming Up!

April:
Focal Therapy