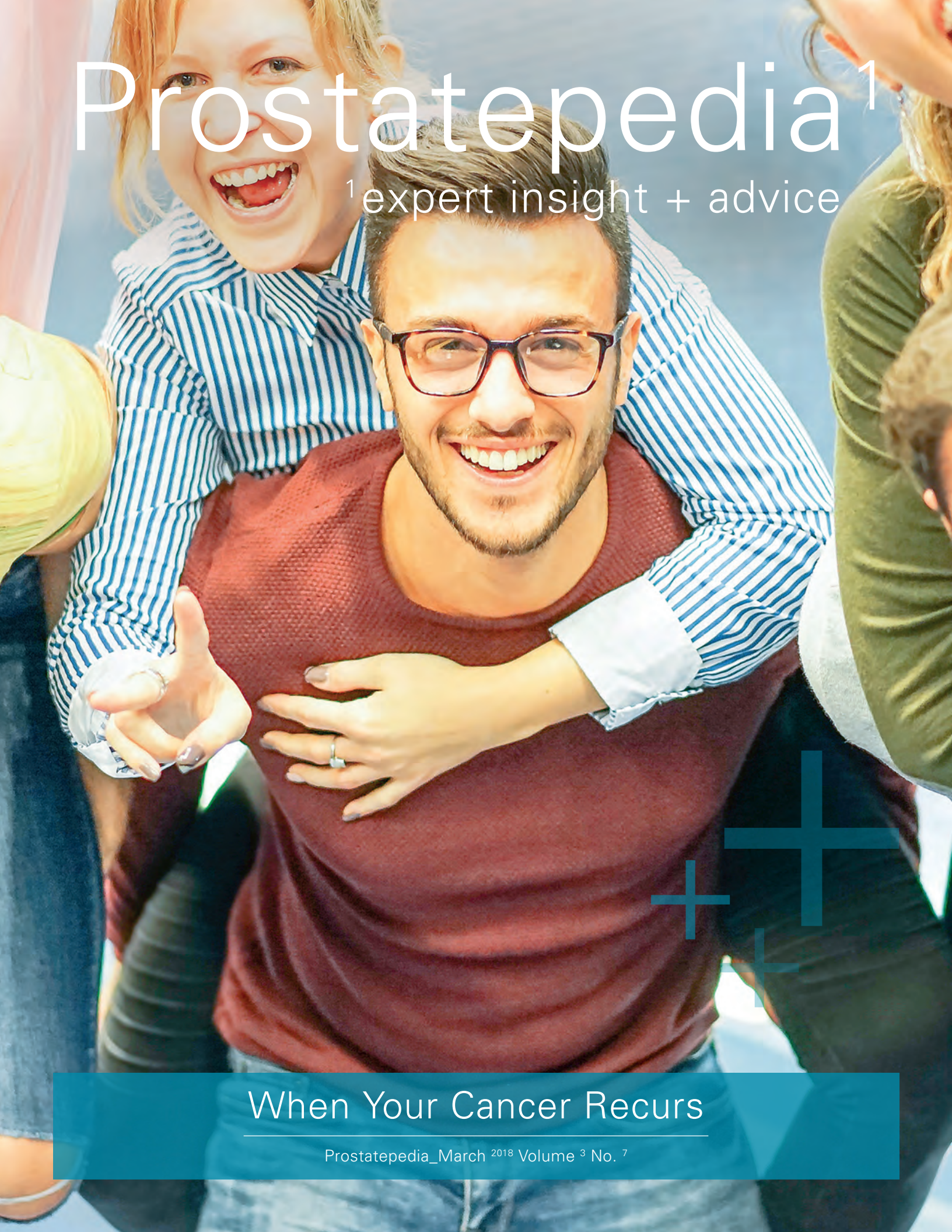

Prostatepedia[1]

[1]expert insight + advice

When Your Cancer Recurs

Prostatepedia_March [2018] Volume [3] No. [7]

In this issue....

In March, *Prostatepedia* focuses on your options when your prostate cancer comes back after initial surgery or radiation.

As I reviewed the various conversations, I could not help but note how views have evolved in recent years. Until quite recently, it was widely assumed that men with prostate cancer recurrent after surgery or radiation had widespread metastatic cancer, even if it was not yet apparent on imaging studies. This assumption naturally led researchers to focus on developing systemic treatments capable of attacking the cancer throughout the body.

Today, that assumption is being challenged by the idea that there are men who have metastatic cancer limited in extent and that they might benefit from surgery or radiation focused on the known metastases. This is called *oligometastatic* prostate cancer.

How did this revolution in our understanding of prostate cancer start? A key scientific paper was published January 1, 2004 by radiation therapists and urologists at University of Rochester (See *Radiation Oncology, Biology and Physics* 58, 3-10, 2004). It has taken a long time for the implications of this important paper to gain acceptance in the medical community.

One of our conversations this month is with Dr. Piet Ost, who has been involved in randomized clinical trials testing the oligometastatic concept. His interview reviews the major issues facing this line of research.

At this point, we know there are patients who received radiation for oligometastases many years ago who still are free of detectable metastases. We do not have adequate tools to determine who will and who will not benefit from treatment directed at oligometastatic disease. We also do not know the best radiation or surgical approaches to various metastatic sites.

For many years, we depended on bone and CT scans to detect the presence of metastatic prostate cancer. These imaging techniques were known to be relatively insensitive and missed smaller metastases, but were acceptable when the treatment options were only systemic drug treatments palliative in nature.

Once you concede that there are men who might benefit from treatment directed at their oligometastatic disease, it becomes much more important to know exactly where the metastases are so that you avoid treating men with widespread metastases as if they had oligometastatic disease.

This explains why the medical community is so interested in improving our imaging tools to detect prostate cancer metastases. This month, you'll also read several interviews discussing this line of research, especially those focused on the PSMA scan.

There have also been dramatic improvements in how we treat men with more widespread metastatic disease. Dr. Charles Ryan provides a comprehensive review of the current and likely future options. I would also point out that he has a very interesting new book *The Virility Paradox: The Vast Influence of Testosterone on Our Bodies, Minds, and the World We Live In* currently available for preorder on Amazon. (http://a.co/4XnTMal)

Finally, Dr. Eric Rohren reviews the use of Xofigo (radium-223). The appearance of this radioisotope revolutionized the management of metastatic disease in my own clinic. I found his comments very interesting; I'm sure you will as well.

Charles E. Myers, Jr., MD Pp1

ISSN: 2381-4020

Prostatepedia is published in Charlottesville, Virginia by Rivanna Health Publications, Inc.

Contents:

Contributors:

Editorial + Billing Offices
274 Redwood Shores, #739
Redwood City, CA 94065
(800) 975 6238

Administrative Offices
PO Box 655, Earlysville, VA 22936

Guest Commentary
Alicia Morgans, MD

Dr. Alicia Morgans is a medical oncologist at the Robert H. Lurie Comprehensive Cancer Center of Northwestern University in Chicago, Illinois. She specializes in treating advanced prostate cancer and is particularly interested in addressing treatment side effects.

She frames this month's conversations about prostate cancer recurrence.

One of the most common questions I'm asked as a doctor who treats prostate cancer is: *what happens to me if my cancer comes back?* This is always a difficult conversation, especially because people often ask it in the presence of their family members. A man's wife or child is also really interested in knowing the answer to the question. The question is often driven by anxiety and fear in men who have already undergone what can be a life-altering treatment experience. They're trying to look ahead and plan for their future. But there are many parts to any possible answer.

First: *what do you go through to monitor before the cancer comes back?* After treatment, we follow a man's health, watch his PSA intermittently over time, and often do imaging studies.

If the cancer comes back, the first sign is often that a man's PSA starts to rise. At this point, we typically use imaging studies to understand what the disease is doing. Even when the PSA is really low, our new imaging technologies can show us where the cancer is and help us determine how a man's recurrence may be ultimately treated—whether that is with local or systemic treatment. Again, this is a really anxiety-laden situation. We're fortunate to have these new exciting imaging technologies for patients and their clinicians, which *Prostatepedia* discusses at length in this edition.

We use these imaging technologies in men with biochemical or PSA-only recurrence to help us understand where the cancer is located. For some men, these new imaging techniques might show us that there is a cancer recurrence in the pelvis where radiation can be given to potentially cure them of recurrent prostate cancer. That is a huge win, progress for our patients, and of course, wonderful news for the men and their families.

For other men, it is possible that we will not necessarily find recurrence, even with new imaging techniques. In those cases, we often continue to wait and watch. Biochemical recurrence can be challenging psychologically because knowing that your PSA is rising can be stressful, and the data explaining the best approach to treatment is not complete.

For men who have a single area of prostate cancer that has come back, whether as a single bone lesion or a few locations, advances in therapy for oligometastatic disease have come fast and furious. In this issue, Dr. Piet Ost talks about oligometastatic prostate cancer and how we might use radiation or surgery to treat a small amount of recurrent prostate cancer. Several clinical trials are working hard to figure out if treating this low volume of prostate cancer in single areas will potentially cure men of recurrent cancer.

It's really important that we have new treatments we can use for men with hormone-sensitive metastatic prostate cancer, too. Over the last few years, we've seen men with metastatic hormone-sensitive prostate cancer live well for many years with several options for treatment. New data describing chemo-hormonal therapy or androgen deprivation therapy (ADT) with Zytiga (abiraterone acetate) have been incorporated quickly into clinical practice and are being widely used to help men with metastatic hormone-sensitive prostate cancer live longer.

Unfortunately, sometimes a man's prostate cancer comes back more broadly, as a rising PSA only, or with sites of metastatic disease. This can be challenging physically, because sometimes it's coupled with fatigue or pain as well as emotional difficulty. The cancer that a man thought was gone has now come back. To address this, there are many scientists and physicians working to try to help men with prostate cancer live better by using therapeutic advances as well as psychosocial and pain support teams that can improve patient-reported as well as disease outcomes. By incorporating social work and psychiatrists, centers are able to support men and their families, helping patients cope with PSA anxiety, which is an issue that can be anxiety-provoking and potentially go on for years at a time.

In terms of therapies, we as a field are very excited about new data that offers new therapies to men with biochemical recurrence who develop castration resistance before they have radiographic evidence of metastatic disease. Two clinical trials presented last month in San Francisco at the annual ASCO Genitourinary Oncology Symposium suggest that using either Xtandi (enzalutamide) or Erleada (apalutamide) —both androgen receptor-directed therapies—can prolong metastasis-free survival for men with castration-resistant non-metastatic disease. This is a valuable advancement because any day spent without metastasis is a day spent feeling stronger and with less pain. We are also excited because both of these oral drugs have relatively low toxicities. Both clinicians and patients win when we add a significant amount of metastases-free time with a few pills and minimal side effects.

As a clinician, I understand the anxiety that drives the question: *what if my cancer comes back?* But this is a time of incredible hope. Medical advances are helping men live longer and live better, even if their cancers do come back.

Phillip Koo, MD
Imaging Recurrent Prostate Cancer

Dr. Phillip Koo is Division Chief of Diagnostic Imaging at the Banner MD Anderson Cancer Center.

Prostatepedia spoke with him about imaging recurrent prostate cancer.

Why did you become a doctor?

Dr. Philip Koo: I became a doctor in large part because I couldn't imagine anything better than spending my life learning about the human body and using that knowledge to improve human health. Given that I tended to do better in science and math, medicine provided a nice fit.

"We really need to prove why this is important."

Why radiology?

Dr. Koo: During medical school rotations, you try a variety of specialties. A common theme in all my rotations was the central value or importance of imaging within the care of a patient. That piqued my interest in radiology. When I learned about radiology, I was captivated by looking at images or different techniques to capture a certain body process anatomically or physiologically and by being able to use that information combined with the clinical scenario in order to come up with a diagnosis.

Did you ever study engineering? I've been reading a lot about how radiology and imaging are becoming incorporated into the tech world, such as with IBM Watson.

Dr. Koo: I'm not much of a techie. Before I switched to one of those flat screens, my friends used to joke that I was the last person in the United States to have a tube TV.

To me, it's not necessarily a disconnect with radiology because radiology is the practice of medicine. It is an art. No matter how much technology we implement, there still is an art to the way you practice the science of radiology.

There is no question that technology has caused a tremendous growth in our field over the past 10 to 20 years. These technologies were disruptive and beneficial to our specialty. Artifical intelligence and machine learning are the newest technologies poised to disrupt the specialty. As a specialty, we are embracing these tools and finding ways that they can be utilized to improve patient care.

What kinds of imaging techniques are men with prostate cancer likely to encounter?

Dr. Koo: The biggest players in the imaging of prostate cancer are MRI, bone scans, and CT scans.

MRI is typically used to evaluate the prostate gland itself while also visualizing surrounding structures and pelvic lymph nodes.

A bone scan is a nuclear medicine scan that images your whole body. It looks for bone metastases. Usually at initial diagnosis, it's reserved for patients with intermediate or high-grade disease. We use it in patients with biochemical recurrence and also in patients later on in the disease.

CT scans send radiation particles through the body to look at bones and soft tissues. We typically give intravenous contrast because it helps us diagnose lymph nodes and any metastases that might be in organs like the liver. CT scans can also pick up bony lesions. Typically, the bony lesions in prostate cancer are sclerotic, so using the CT and bone scans together really helps us be more sensitive and specific in diagnosing bony disease. That's why you'll often get both exams together.

Some imaging occurs when men are first diagnosed. When, after treatment, do they encounter these newer imaging techniques? After a high PSA reading? Or just a part of routine follow-up?

Dr. Koo: That's a really tough question because imaging has a role throughout the continuum of care for any prostate cancer patient. Screening currently isn't done with imaging, but there are a lot of research studies looking at it.

Prostate MRI is most often used for the detection of local disease. Oftentimes, patients with a rising PSA and a negative standard biopsy might get an MRI or an MRI-guided biopsy.

Bone scans and CT scans are used to help detect metastatic disease. There are many different scenarios, but usually after patients are diagnosed with cancer, most will visit radiology if there is a suspicion for metastatic disease. If we refer back to the RADAR 1 paper published in 2014 by Dr. Dave Crawford in *Urology* (see *Urology* 2014 Mar; 83(3):664-9), we talk about imaging patients at initial diagnosis and imaging those who are intermediate or high-risk. In those patients, we recommended a bone scan and a CT scan.

Patients who are biochemically recurrent may also be imaged. Again, MRI will often be used to look for locally recurrent disease. Bone scans and CT scans are used to look for metastatic disease.

What about some of the newer imaging techniques?

Dr. Koo: The newer techniques are exciting. In both the patient community and the scientific community, we've heard a lot about these tools over the past decade. They weren't widely available, especially in the United States. These newer imaging tools are simply better, which is why there is so much excitement. They will pick up more sites of disease at lower PSA levels.

When we do detect sites of disease, they're more specific. Our confidence that these sites are actually disease is higher than our confidence when we're using traditional bone and CT scans. These tests perform at a higher level compared to standard imaging.

Another benefit to these new tools is that in one single exam, we'll be able to detect soft tissue and bony disease.

How do these newer techniques change treatment? If you can pick up the disease at a lower PSA is that going to change how a doctor treats a man?

Dr. Koo: Yes. We will be able to detect disease sooner. Currently, these newer imaging techniques are used mostly in patients with biochemical recurrence. When a patient has biochemical recurrence and we see the PSA rise, our standard imaging techniques are often not good enough to detect metastatic disease. The problem is that the radiation oncologist or the urologist needs to decide how they want to treat the patient.

Using these newer tools, we can provide the urologist or radiation oncologist with better information about whether or not the disease has spread at the time of biochemical recurrence. If it has not, and the urologist can perfrom salvage cryotherapy or a radiation oncologist does salvage radiotherapy, we could potentially cure the patient.

Really?

Dr. Koo: You're hitting the disease before it spreads, so theoretically yes. These newer imaging techniques do better, but we really need to prove why this is important and how this impacts care. The answers to these questions will solidify the utility and value of these imaging techniques for prostate cancer patients.

If a patient gets the Gallium-68 PSMA or Axumin scans will his local urologist or oncologist know what to do with that information?

Dr. Koo: Maybe. The problem is that all of this sounds great: we have a tool that can detect disease sooner, better, and more accurately. But then the more important question is what to do with that information and does it impact outcomes. If we don't know, then what is the value of that imaging tool?

We operate under the assumption that earlier detection is always better, but we're learning that in a lot of diseases that is not always true. We could be over-diagnosing and over-treating certain diseases.

Whether it's imaging, urology, radiation oncology, or oncology, it really is a team effort because we all bring something unique to the table. We really need to work together to make sure we come up with the best plan and the best answers.

What are some of the obstacles to determining what to do with the information? What needs to happen next?

Dr. Koo: We want to detect disease sooner, treat patients appropriately, and then more importantly, see these patients live longer. If they're living longer until their first progression, that is also a victory.

We need more studies with the appropriate methods that will answer those questions and prove that earlier detection and treatment lead to longer survival.

The problem with these trials is that patients with biochemical recurrence will go on to live very long lives afterwards. Collecting data over that long period is difficult. I don't think we have the time to wait 10 or 20 years before we start acting, especially since these better tools are available now.

What would you say to a man reading this who has a biochemical recurrence? Is it worth it for him to get the Gallium-68 PSMA, or is it better to make sure his doctor is onboard and knows what to do with the information beforehand?

Dr. Koo: Every patient with biochemical recurrence should have a discussion with his urologist regarding the availability and value of one of these newer tests. They should have an open discussion about how they would manage positive, negative, or indeterminate results.

Knowing whether or not a patient has metastatic disease is very powerful.

Will there ever be a scenario in which we're using these highly sensitive tests in initial diagnosis and screening?

Dr. Koo: Currently, these tests have no role in screening. However, in a newly diagnosed prostate cancer patient with a high Gleason score and high PSA, whose imaging tests are negative, and whose urologist still suspects he has metastatic disease, these tests will detect metastatic sites much better than before.

Another patient group that might benefit are those diagnosed with castration-resistant prostate cancer (CRPC) and *no known* metastatic disease (M0). These patients are often held in a holding pattern because many of the new therapies that have been approved for patients with CRPC are only approved for those with *known* metastatic disease (M1). This space is changing as new therapies are being developed for M0 disease. Stay tuned.*

RADAR 1 (see Urology 2014 Mar;83(3): 664-9) helped address the M0 CRPC scenario by providing recommendations for when and how to image these patients. These newer imaging techniques will diagnose metastatic disease sooner, so there is potential value to using these tools to diagnose patients with metastatic disease.

Are there parts of the world where these sort of tests are more readily available?

Dr. Koo: PSMA-based PET imaging is more widely available in Europe, Brazil, and Australia, but it's not very widely available in the United States. In the United States, these agents are still investigational; there are several sites offering this test under IND expanded access programs.

In the United States, however, we do have recent approval of a radiotracer called Axumin. The generic name is fluciclovine. Most people would agree that PSMA might be a little better. However, Axumin's performance is better than anything else we've had in the past in the United States.

There was one study that showed it performed as well if not better than C11 Choline, which many are familiar with. To me, it's not necessarily important which specific test you get. The more important question is whether you should get one of these advanced imaging tests. Then, decisions can be made based on what's available and whether or not you have access to a PSMA, Axumin, or Choline PET/CT exam.

One option is for patients to join a clinical trial looking at these scans, right?

Dr. Koo: Correct. However, there aren't that many clinical trials using these scans. There are some trials using Gallium-68 PSMA, but they require patients to pay out-of-pocket for the costs of the radiopharmaceutical and the imaging. The data collected from these trials will help lead to approval of Gallium-68 PSMA in the United States.

Why do you think there aren't more trials?

Dr. Koo: That's a difficult question to answer. The trials are expensive and there is less financial support for these diagnostic trials compared to therapeutic trials. Even if a trial proves superior performance of a diagnostic tool, reimbursement remains a major concern. And without adequate reimbursement, these tools won't be sustainable in the marketplace. Increased focus on outcomes data will be important to demonstrate the value of these imaging tools.

Do you have any advice for men reading this who are considering advanced imaging?

Dr. Koo: We've been talking about better imaging tools for prostate cancer for years. When it comes to other cancers, we moved forward a great deal when FDG PET/CT became available.

With prostate cancer, we've been stuck with CT and bone scans since the 1970s. They're great tools. I don't want to devalue what they've done for our patients since then, but we knew we could do better. Urologists and oncologists knew patients had metastatic disease, but our imaging tools limited detection.

We have new tools available to us in 2018. There is no question that costs are going to be higher, but that shouldn't stop us from exploring and pushing the envelope. The whole purpose is to improve overall survival and treatment for our patients.

An ounce of diagnosis could be a pound of cure. If we could identify disease sooner, identify the right patient for these exams, and use them at the right time, then we could probably create treatment plans more appropriate for patients with better outcomes. It's something that I firmly believe. There is so much potential here.

Is there anything else you think patients should know about imaging?

Dr. Koo: When radiology is practiced in a vacuum, it's not as powerful as when it's integrated into patient histories and treatment plans. Radiology is a very powerful tool. But we often think of it as a commodity, something that does not have any distinguishing value. That is a huge under-estimation of radiology.

When performed correctly in a multi-disciplinary setting, with access to the medical record and physicians who are taking care of the patient, radiology unlocks information that can really impact care for patients with prostate cancer. And we are currently only scratching the surface. This will change as analytic tools continue to analyze bigger data sets that include imaging and clinical data.

If a urologist determines that their patient needs imaging, they're going to write a request for imaging that describes what type of test they want and why they need it. Patients often go to the closest facility. Convenience is important, but when it comes to certain tests or exams, I urge patients to seek out subspecialized radiology experts and facilities with the experience and expertise in the performance and interpretation of the exams. Pp[1]

** Erleada (apalutamide) has since been FDA approved for nonmetastatic castration-resistant prostate cancer patients.*

Eric Rohren, MD
Imaging + Radium Therapy

Dr. Eric Rohren is the chair of the department of radiology at Baylor College of Medicine.

Prostatepedia spoke with him about imaging for recurrence and using Xofigo (radium-223) to treat bone metastases.

Why did you become a doctor?

Dr. Eric Rohren: I actually tried my best not to become a doctor initially. My father was a doctor. I grew up in the shadow of the Mayo Clinic up in Minnesota. I knew I was interested in science, but for a long time, I thought I wanted to pursue a career as a research scientist and not a physician.

As I made my way through college and looked at what I really enjoyed and what a career would look like, I wanted to focus on patient care and do things that impacted people. I looked for a career that could combine the science that I enjoyed with the ability to directly interact with people, to hopefully make their lives better. I came full circle, landing back in a career in medicine.

How did you end up in radiology and nuclear medicine?

Dr. Rohren: That was also a little bit indirect. Most medical students aren't introduced to radiology until very late in their medical training. A lot of people make the decision to do medicine or surgery well ahead of time, but radiology is often a latecomer. Nuclear medicine is even more so. It's a subspecialty of imaging, its own medical specialty, but it can also be considered a part of radiology. Medical students often make it through their entire medical training without learning about nuclear medicine at all.

I was fortunate to have a mentor in the radiology department at the Mayo Clinic who taught me what he loved about radiology and how impactful it was on patient care. He got me further plugged in to nuclear medicine.

As I went into my residency and pursued it further, I decided that the science that I loved and the ability to do new things were most focused in radiology, and particularly in nuclear medicine. That's the career I ended up with.

Many people assume radiology is just imaging. Is that the case? Where does it branch off into nuclear medicine? What kinds of therapies would a radiologist administer?

Dr. Rohren: A big part of being a radiologist is reading images. We also oversee the acquiring of the images, so we monitor the acquisition of the scans and the technologist performing the scans. Many of the people reading this article will have had X-rays, CTs, and MRIs. While technologists and nurses take them into the scanner and get them positioned, ultimately, the radiologists are the ones who oversee the program and make sure that the scans are acquired in the right way. They're responsible for patient safety, the patient's experience, and things like that.

At the back end, once the scan is complete, radiologists interpret the scans and look for the findings that may be used to guide medical decisions. Whereas many radiologists can go through their day and not see a patient, they do see the patient's images. However, there are components of radiology that are directly related to therapy and directly patient-facing.

In interventional radiology, we do biopsies and endovascular procedures, catheter-based procedures, embolizations, administering treatment, and things like that. In women's imaging such as mammography and breast cancer screenings, those radiologists spend a lot of their time talking to patients and counseling them about their diagnosis and procedures.

One area of radiology where we do meet with a patient face-to-face and interview or talk with them is in nuclear medicine. In that role, we act as "real doctors," where we walk in, interview the patient, review their labs, go over the plan, do a consent process if it's for a therapy that has some risks associated with it, and then we administer the therapy directly there in the clinic. When I serve in that role, I feel much more like a patient-facing physician than I do a traditional radiologist. It's one of the most enjoyable things about it for me.

People tend not to be familiar with specialists until they need them. They might not really understand what you do until they're at the point where they need your services.

Dr. Rohren: Generally, that is the impression, that the radiologist sits in a dark room, reads scans, and that's the end of it. The national societies for radiology really encourage us to interface with patients and physicians to make our presence known. Radiologists need to do a better job of that.

We have a critical role to play in the management of patients and the diseases that they're dealing with, so the more we can be out there, share our professional knowledge, act as consultants, and act as physicians for the patients, that's a positive thing.

In terms of imaging, what kinds of scans can determine if a man has metastases (mets) anywhere in his body?

Dr. Rohren: X-ray has been around for a long time and still has a role to play. It's easy to obtain, it's cheap, and it has low radiation exposure. We still rely on a good old-fashioned chest or bone X-ray, depending on the patient's symptoms.

These days, most patients with any type of malignancy, and specifically prostate cancer, are managed in a couple of ways. One way is a CAT scan. CAT scan is a 3-D imaging technique that uses X-rays that can take images of the body, chest, abdomen, and pelvis. Most patients with newly diagnosed prostate cancer or treated prostate carcinoma have undergone a CAT scan at some point in the course of their disease. CAT scans can show us the prostate gland, lymph nodes, liver, and many of the different organs where cancer may be hidden.

To supplement that, patients with prostate cancer often get a bone scan, which is a nuclear medicine technique. In a bone scan, we inject radioactive material that goes to the skeleton, and most strongly so in areas where there's increased skeletal turnover, where something in the bone is inciting a reaction. It may go to benign things like healing fractures, arthritis, and various areas of injury. But the radioactive material also goes to areas of metastatic disease in the skeleton, and it localizes most particularly in those areas, lighting up on these bone scans.

Rather than just a particular region of the body, a bone scan shows us from the top of the head all the way down to the feet, which is nice. We get a look at the entire skeleton, and we can look for the little spots that are lighting up that may indicate the presence of metastatic disease in the skeleton.

CAT scans and bone scans are very widely used. A bone scan is a little bit better than a CAT scan in looking for these bone metastases, so the two really augment each other in detection of the disease.

Beyond these, we do have some newer imaging techniques coming into play. There's a way of doing a bone scan with a PET scanner. A PET scanner is another nuclear medicine technique that is more sensitive than a standard nuclear medicine camera, and it acquires a CAT scan at the same time. You can look at the images on the nuclear medicine technique overlaid on the CT scan to see where exactly the activity is and what it's due to.

We can also use some agents with PET scanning to look at the skeleton. A so-called fluoride PET/CT bone scan seems to have many advantages over a conventional bone scan in terms of detecting smaller disease, more sites of disease, and things like that.

MRI is also used in some cases. Traditionally, MRI is used to evaluate specific areas, so if there's pain in a particular area such as the skeleton, MRI is a great way to do that. MRI is also used to look directly at the prostate gland and at the prostate bed after prostate surgery or after other therapy in the pelvis. It can be very good at detecting small volumes of disease.

The problem with PET scanning and MRI scanning is that they are less accessible, although MRI is in most places now, and most major areas have access to a PET scanner.

Then there's the issue of cost. Both techniques are costly. We need to determine if the added cost is justified by the additional information that those scans provide.

Beyond these techniques, the exciting thing for nuclear medicine is the new developments on the horizon. As we discover more about the molecular nature of disease, why cancer forms, and what makes and defines a cancer cell, those molecular discoveries can be translated into imaging studies that we can then use with PET scanning to be even more sensitive for detection of disease.

For example, there are several new molecular tracers in the United States that are approved for imaging of prostate cancer. Choline and Axumin (FACBC) are both agents approved in the United States for use with PET/CT.

Internationally, people are moving to a compound called prostate surface membrane antigen (PSMA) that can image prostate carcinoma. It seems to be even better than Choline or Axumin. The data is still a little bit undetermined at this point, but there's a lot of excitement around these newer agents being able to seek out cancer in very small volumes anywhere it occurs in the body.

Then I guess the question becomes: when do you treat?

Dr. Rohren: Yes. That is very much the question. As we discover more and more sites of disease and smaller sites of disease, the question becomes: do we need to treat those aggressively or conservatively? We're discovering new things about tumor biology, and we need to understand how that gets translated into the best appropriate therapy for patients.

Are some of these different imaging techniques traditionally used to initially diagnose men and some used in men with an increasing PSA after a primary treatment? How do you decide which technique to use when?

Dr. Rohren: I think there's a role for imaging in both of those settings. We know a lot about the natural history of prostate cancer, so for patients who present with fairly early-stage disease, we can determine that with clinical workup, PSA values in the blood, and things like that. We know what the overall prognosis is based on the biopsies in that early information.

Imaging can play a role in the early stages, but mainly we use it to confirm that the disease is localized to the prostate gland or pelvis, and that there's nothing unexpected elsewhere in the body that might change your initial management.

Imaging really comes into play more so in the setting of biochemical recurrence. There you have a patient who has undergone initial treatment. They may go for a period of time where their PSA remains undetectable and everything looks good, but then the PSA starts to creep up. When that happens, you're pretty certain that there's recurrent prostate carcinoma somewhere in the body and need to discover where the cancer is so you can decide how best to treat it.

That is where imaging really comes into play: when we need to look for sites of recurrence after initial treatment. Imaging is really the only way to discover where recurrence is located, so that we can decide whether there might be a role for radiation therapy, radionuclide therapy, surgery, or standard chemotherapy. Imaging is the best tool to determine that.

What is Xofigo (radium-223)? How do radiologists in nuclear medicine use it? And why is it so much more effective than previous treatments?

Dr. Rohren: Radium chloride is a radioactive compound. In the early part of the 20th century, radium was used to make the hands of watches glow in the dark. But the women painting the radium onto the watches in the factories got very sick. They were called the *Radium Girls*, and they developed cancers because they were using a compound of radium that lasted thousands of years. It got into their body and just sat in their bones, causing cancer. Because of this, radium had a bad name for a number of years.

There are compounds of radium that are safer to use. To understand this, we need to review a little bit about molecules in general. Elements come in various forms and while some are stable, some of them are radioactive. Radioactive elements, or radioactive compounds, have different properties. One of those is called the *half-life*: that refers to how long the radioactive compound sticks around. Half-life generally means the amount of time it takes for half of that radioactive compound to decay away. After a certain amount of time, half of it will be gone, and then another half-life will go by. Now you'll be down to a quarter, then an eighth, a sixteenth, and it'll keep on going down: halving.

The radium that we use for treatment these days has a half-life of about 11.5 days, so it's a much shorter half-life than the radium that caused problems back in the early 20th century. It was developed in Norway as part of a program in conjunction with the Norwegian Radium Hospital. They were looking for medical uses of radioactive materials.

There is a long precedent for this. We've been using radioactive iodine to treat patients with overactive thyroid glands and thyroid cancer for decades.

They were looking for ways to use radioactive compounds to treat malignancies and came across this compound of radium called radium-223, which has a half-life of a little more than 11 days. When it decays, it emits radioactive particles into surrounding tissues. Those radioactive particles can cause local tissue damage. It breaks up the DNA, it prevents the cells from dividing, and it can ultimately cause cellular death. The other nice thing about radium, and the reason it works, is that radium behaves chemically like calcium.

The skeleton is composed of some biologic material, but calcium is a major component of our skeleton. Calcium deposits in the body seek out areas of the skeleton where there is increased turnover in the bone and irritation to the skeleton, which includes areas where there is metastatic disease. When we administer the radium, it behaves just like calcium. It circulates around the body, but it will end up most intensely in the skeleton where there is metastatic disease. Then, it sits there and undergoes radioactive decay, emitting radioactive particles and causing local tissue injury to the cancer cells. As a result, it treats the metastatic disease that is residing in the skeleton.

Is Xofigo (radium-223) used in people who only have bone metastases, or can you use it in men with bone metastases and also, say, a lymph node met? Does it do anything to those mets in the lymph node?

Dr. Rohren: Yes. We're not restricted to using Xofigo (radium-223) only in patients who have disease confined to the skeleton. According to the recommendation of the manufacturer, Xofigo (radium-223) only treats disease in the skeleton.

With that said, you can treat a patient who has say some lymph node metastases and some disease elsewhere so long as you recognize that you're really using the Xofigo (radium-223) to treat the disease in the skeleton and not the lymph node.

The company says you should not use Xofigo (radium-223) in patients who have visceral metastatic disease—liver or lung mets.

It's not that the Xofigo (radium-223) will *harm* those patients; it's just not doing anything to *help* them. Disease in the liver or the lungs is much better treated with chemotherapy than with radium.

You would just be wasting time by using the Xofogo (radium-223)?

Dr. Rohren: Yes, exactly. We want to take care of the disease that's the most clinically relevant, and in most cases, it's the liver disease, lung disease, etc. Bone disease tends to grow more slowly.

If a man only has one metastasis, can he still use Xofigo (radium-223), or does he have to have more than one met?

Dr. Rohren: There isn't a threshold. We have a window of opportunity with Xofigo (radium-223). When prescribed, Xofigo (radium-223) is given in six doses, a month apart because the initial approval for Xofigo (radium-223) was for a six-dose cycle. Some studies that are just now being performed suggest that an additional six courses may be administered safely in patients who responded well to a first course. It's not a fully approved indication yet, but the early research suggests that may be possible.

Nevertheless, the number of doses administered for Xofigo (radium-223) is limited; it's not something that patients can get every month for the rest of their lives. We could give it early, and a patient with a single known metastasis may indeed benefit from radium therapy.

But my concern in that case is that if we give Xofigo (radium-223) at that point, and the man develops additional bone metastases in the future, we would have used the opportunity for therapy and wouldn't be able to give the Xofigo (radium-223) again. We need to wait for the optimal time.

One bone metastasis is probably too early for radium, unless that met is very painful, or there are other reasons you might want to treat it. A better use of Xofigo (radium-223) is probably in the range of five to ten bone metastases.

On the other hand, when Xofigo (radium-223) was first approved, we waited too long. We were waiting until patients had *a lot* of bone disease in the skeleton. Giving the radium at that point, when they're developing liver and lung mets, is too late, and we don't get its maximum benefit.

That is actually a critical question that has yet to be determined. What is the best timing for Xofigo (radium-223)? When should you give the radium in relationship to some of the other therapies that are available?

If a man has one met, couldn't you assume that there are maybe other mets that are just still too small to see? Like micrometastases*? Do you think Xofigo (radium-223) would knock out those micromets?*

Dr. Rohren: That's a really interesting question. We have a lot more to learn about it. Xofigo (radium-223) goes to the areas that incite enough of a reaction in the skeleton to give you that bone turnover so that the radium can get there in the first place. Xofigo (radium-223) is not going directly to the cancer cells. It's going to the bone around the cancer cells based on the reaction that the cancer is causing.

These microscopic metastases probably don't have enough bone reaction to be able to incite enough radium localization to really affect a therapy. It does go to the skeleton, so to a certain extent, there is radium throughout the skeleton after one of these therapies. Maybe that overall radiation from the radium administration is enough to treat those microscopic metastases.

You've hit upon a fascinating question. I wish we knew the answer. We need more research to understand the optimal timing of this therapy and whether this can be used to prevent the development of bone metastases down the road.

You said there are six doses of Xofigo (radium-223) and that there is some evidence that an additional six doses might be effective. What if a man starts to respond in three or four doses, does he have to keep going and get all six or can he stop early?

Dr. Rohren: We looked at that and found that men who completed the full six doses had a better outcome than those who stopped early. That's not to say that you wouldn't look at things on a case-by-case basis, but I would encourage patients to plan on completing all six doses.

The only reason to stop early would be if your blood count started to drop. If there were some reactions to the radium that the patient just couldn't tolerate, we might consider delaying a dose, stopping the course, or moving on to a different therapy.

The first two doses tend to have the most side effects. Once you make it through those first two, the subsequent doses generally go pretty smoothly and are tolerated well.

What kinds of side effects might a patient encounter?

Dr. Rohren: There are three main side effects that we can expect on a course of Xofigo (radium-223). The first one is the blood counts. Any radioactive compound that gets into the body can have an effect on the bone marrow. Bone marrow is at the center of our bones, and it is where red and white blood cells are produced.

When the radioactivity gets into the skeleton, most of the radiation is delivered very close to the radioactive decay site, which is both in the outer surface of the bone and in the main part of the bone. The radioactive particle that Xofigo (radium-223) emits, called an alpha particle, only travels a short distance before it deposits and causes an effect. It's less than a millimeter from the site, which is good.

Nevertheless, a small amount of the radioactivity has an impact on the bone marrow in the center of the bone. After Xofigo (radium-223) treatment, it's not uncommon for the blood count—the hemoglobin, the white blood cell count, and the platelets—to dip a bit. Around ten days to three weeks after treatment, you can get a little bit of a dip in the blood counts.

We do need to be sure that the blood counts are above a certain level before we start radium therapy. Then, each time the patient comes back for a subsequent treatment, we check the blood counts again to make sure that they're good enough for that next dose. If they start with adequate blood counts, almost all the patients will do fine. The blood counts may dip a little bit and then they recover. They can go on and get their six doses.

However, we do see blood counts dip in some patients, and they may not recover quite enough by the time they come back. We have a couple of options in that case. We can delay the next treatment for a week or two and wait for those blood counts

to recover. Often they will, and then they can get their subsequent doses.

We may stop radium therapy if the blood counts go down, and they're not able to recover to a certain point. We don't want to damage the bone marrow to the extent that it can't recover.

The other two side effects are symptom related.

Radium can cause some gastrointestinal upset and in many cases diarrhea. Most of the radium that we give localizes in the skeleton, where we want it, but the leftovers circulate around the body, get eliminated through the colon, and come out in the feces. The radioactivity in the colon can irritate the colon lining causing some gastrointestinal upset, upset stomach, diarrhea, or constipation. Many will experience gastrointestinal issues. They'll notice a mild change in their gastrointestinal pattern about two days after the radium is administered. It might last for about a week. Very seldom does it require additional fluids or anything like that, and it's only problematic in a few cases.

The third potential side effect is an increase in bone pain over a short period of time, a so-called *flare phenomenon*. Men are often aware of this because they have had other therapies that have caused the same thing, but it can really happen quite strongly with radium.

I counsel men ahead of time about bone pain because I don't want them to get the radium, go home, and then two or three days later if they really start to hurt, they think that the radium is not working and that the disease is getting worse. That's actually the radium working and the cancer responding to radium therapy.

It's important to realize that this can happen and to take medication to help with the pain. Men with prostate cancer are tough. They've been through a lot. They're not complainers. They go home, start hurting, and they don't do anything about it. They just hurt more and more. I want them to take pain medication: Advil, Tylenol, or something stronger if they need it.

> *"There's a lot of excitement around these newer agents."*

In my experience, about two thirds of the men that I've treated with radium will have this sort of a flare response in the first or second dose. It can sometimes be quite severe. I've had men who have had to go into the emergency room to get a shot of some strong narcotic to help with that pain.

From years and years of treatment of bone metastases with radioactive material, the good news is that the men who get that flare response generally have a better outcome. That means their cancer is responding to the therapy and this is actually a product of that response.

That flare response is most severe with the first dose, though we sometimes see it with the second dose. Very rarely do we see it with the third dose, and almost never do we have it with the remaining three doses. By that point, things have quieted back down, and we are no longer getting that flare response.

Within three or four months it would die down?

Dr. Rohren: Yes. It's very cyclical. It happens again starting two days or so after the therapy, may last a week or so, and then subside. Then they get the next dose. They may get a little bump, but it's not lasting that entire time. It happens during that first five or six days after the treatment and then it gets better.

How do you know if the therapy works? Do you use imaging?

Dr. Rohren: When we start a course of radium, we intend to finish the course of radium. There's not a whole lot that would make us stop. There are no guidelines for this, but I prefer to get imaging halfway through the radium therapies. Other people might disagree and wait through the entire course of radium before imaging. It depends on the patient and how much disease they had to start with, but six months is a fairly long period of time to go without looking to see how things are doing.

If we take a patient who has only about five or six bone metastases, it may be appropriate to get through the entire course of radium, and *then* do an imaging study. I would recommend a fluoride PET/CT bone scan because it has the CT as well as the bone scan information.

In a patient with a more advanced disease, five or six months is a long time to go without looking at anything, particularly when you're not giving anything that can treat disease outside the skeleton. We have seen patients who have been on the radium, and an imaging study after just three doses revealed disease in the liver or elsewhere. We had to take them off Xofigo (radium-223) and get them on chemotherapy.

Depending on the scenario, you can image at the beginning and end of the six radium doses. But I think it is appropriate to do imaging partway through in somebody with more advanced disease who is a little bit higher risk.

We're not using those scans in the middle of the radium therapy to judge what's happening in the bones. That's a difficult thing to determine because, while the Xofigo (radium-223) gets in there and treats the prostate cancer metastases, as the cancer cells die off, the body responds by healing that bone. It heals the bone by depositing more bone in that location. Just like a bone metastasis, it can show up on a bone scan, but in this case it's the healing and not the cancer. That can be somewhat confusing when you look at studies in this stage.

We tend not to read too much into bone scans done in the middle of radium therapy because of that. Again, it's called a flare response. As the body heals those metastases, it can actually make the bone scan look a little bit worse in the short run.

Which combinations of treatments do you think are most effective?

Dr. Rohren: When Xofigo (radium-223) first came out, it was really only recommended as a single agent not to be combined with other agents. Still to this day, we're a little hesitant to combine radium with chemotherapy. It actually says in the package insert that Xofigo (radium-223) should not be administered with chemotherapy.

Under the direct management of a nuclear medicine physician and a medical oncologist, we can do some things that may be a little on the edge. That may indeed be the best route to go for particular patients.

> *"That is what's so exciting about modern medicine."*

The problem is that both Xofigo (radium-223) and chemotherapy can have an effect on bone marrow as well. Combined, the impact on bone marrow can be fairly severe. Early experience showed that when you treat patients with chemotherapy and Xofigo (radium-223) therapy at the same time, blood counts could go down fairly dramatically. That can be a big problem, so we tend to avoid true chemotherapy along with Xofigo (radium-223).

There are some studies coming out now that show a benefit to treating patients with Xofigo (radium-223) and hormonal agents, or bone-stabilizing agents. Some of these other therapies for prostate cancer may not be true chemotherapies, but do have an impact on the cancer. There is evidence that when you treat patients with therapies such as Xtandi (enzalutamide), Xgeva (denosumab), or Zytiga (abiraterone) along with Xofigo (radium-223), they can have an even better outcome than with Xofigo (radium-223) alone. These are relatively early and small studies, but they are leading to bigger trials looking at the optimum combination of radium with other systemic agents.

I firmly believe that the future of treatment for prostate cancer will be combinations that can treat the bone disease with Xofigo (radium-223) and the nodal disease in some of these microscopic sites of disease with other agents that can get in the body to treat the tumor cells directly.

Like a one-two punch?

Dr. Rohren: Exactly.

Is there anything else patients should know about Xofigo (radium-223)?

Dr. Rohren: This is a very exciting time. It's been a privilege for me to be involved in the early phases of Xofigo (radium-223) therapies and to meet a lot of the patients coming in for treatment. There are always new therapies under development and new therapies coming out. That is what's so exciting about modern medicine, and nuclear medicine, in particular.

Just a few years ago, we had no idea that Xofigo (radium-223) was going to be a therapy for bone metastases from prostate carcinoma. Then it shows up, we do the trials, and it has a great impact. It can decrease bone pain. It can improve survival. It's turning into a really good therapy. As we combine it with other therapies, it's probably going to be even better.

We're discovering new things about what makes a cancer cell a cancer cell, what cancers respond to, and finding ways to design therapies that target specific cancer cells with minimum impact on other cells within the body.

I predict that more radioactive and nonradioactive compounds will be developed that will provide new opportunities for patients as they deal with their malignancies. I think it's just a very exciting time.

We're really making a lot of progress and discovering new things about how the body works, how cancer works, how genes work, and all that is being applied to improving patient outcomes and quality of life. Pp1

James Eastham, MD
Surgery for Recurrent Prostate Cancer

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.

Prostatepedia spoke with him recently about surgical options when cancer comes back after initial treatment.

Why did you become a doctor?

Dr. James Eastham: I didn't decide to become a doctor until my third year of college. I was a chemistry major. I had worked in the laboratory and thought I wanted to work more with people. I had a science background and lots of friends who were pre-med. They thought that being a physician would be something that I might enjoy, so I took the appropriate classes and exams and was fortunate enough to get into medical school. That is how I became a doctor.

Why did you choose surgery as opposed to another specialty?

Dr. Eastham: I enjoyed the care of surgical patients. I was very interested in anatomy and how the illnesses that require surgery were, in many ways, based on anatomy. I liked the technical aspects of doing surgery. I liked the hands-on approach and the anatomy that is involved.

Can you define salvage radical prostatectomy for us?

Dr. Eastham: A salvage procedure just means something failed beforehand: a salvage radical prostatectomy is surgery done on a prostate that has been treated with something else. That something else can be radiation. It can be prior high-intensity focused ultrasound, meaning the patient had a heat application to the prostate to try to treat prostate cancer. The something else can be cryotherapy that was unsuccessful. But basically, salvage surgery means surgery after a failed non prostate-removing technique.

"It's just a far more difficult operation for the surgeon."

In what scenario would a man encounter salvage surgery: after a couple of high PSA readings? After another biopsy? After an imaging study?

Dr. Eastham: Most of the salvage surgeries that are done are still done for patients who fail radiation therapy. A patient underwent radiation therapy for prostate cancer. They're followed, and then their PSA blood test starts to go up. Typically, as part of the evaluation for a rising PSA after failed radiation therapy, the patient will undergo imaging studies.

There are different imaging studies that we can do to check if there is any evidence of cancer beyond the prostate. If all of those studies are negative, then the patient will typically have a biopsy of his prostate. If that biopsy shows persistent prostate cancer, the patient is at least a candidate for additional local therapy, meaning therapy directed at the prostate. All of these therapies are called *salvage*. Surgery to remove the prostate is a *salvage* prostatectomy. Some patients may have cryotherapy. That's *salvage* cryotherapy. Patients can have radiation after failed radiation. That would be *salvage* radiation therapy. There are a variety of options.

Is any of this controversial? Or are there any men in whom this kind of approach might be controversial?

Dr. Eastham: The patient should have a cancer that was potentially curable with local therapy at the time of the original diagnosis. The cancer at the time of treatment failure must still be potentially curable with local therapy.

There are some patients who, at the time of their original diagnosis of prostate cancer, had a big, bulky cancer that was treated with radiation therapy and subsequently failed this treatment. These patients really aren't appropriate for salvage radical prostatectomy because they were never surgically curable.

"A salvage procedure just means something failed beforehand."

To be a good candidate for salvage local therapy, including salvage prostatectomy, the patient would have to have been diagnosed with clinically localized, non-metastatic cancer, have undergone a treatment that didn't work, and after initial treatment failure, still have a clinically localized, non-metastatic cancer amenable to local therapy.

As our imaging techniques become more and more refined, are we identifying these recurrences earlier? Does that have any kind of impact on who gets a salvage prostatectomy or not?

Dr. Eastham: Most of the follow up is still done with PSA, so routine imaging is typically not done *after* prostate cancer treatment. Most of the treatments are still based on waiting for a PSA to rise. A rising PSA typically leads to other testing. This other testing has become more sensitive in picking up patients with low-volume metastatic disease. That is where the imaging matters.

If someone already has metastasis, as shown by whatever imaging study, it's unlikely that salvage radical prostatectomy is going to provide them with any particular benefit because this is a big surgery and has potential risks. That is where the imaging comes into consideration. Imaging looks for metastatic disease and basically excludes patients who won't benefit.

Is salvage radical prostatectomy a trickier procedure than an initial prostatectomy?

Dr. Eastham: Absolutely. Any prior treatment to the prostate results in the development of scar tissue. After radiation therapy, high-intensity focused ultrasound (HIFU), or cryotherapy, scar tissue develops. The prostate fuses to organs from which it would typically be easily separated.

The primary concern is the rectum; injury to the rectum is a potentially devastating complication of salvage radical prostatectomy. All of the tissues tend to not heal as well because the scar tissue has an impaired blood supply. There is slower healing. The anastomosis, where we sew the bladder and the urinary tube back together, also tends to heal more slowly. This can lead to a higher risk of urinary leakage, or anastomotic leak. There are higher risks of strictures, or bladder neck contractures, which is scar tissue that develops where the bladder and urinary tube are sewn back together. When that happens, the man just basically can't urinate. There is much higher risk of incontinence.

Again, the radiation therapy results in scar tissue, so things just don't heal as well as they should. On top of that, it's very difficult, even in those men who still have erectile function after radiation therapy, to preserve erectile function in men undergoing some type of salvage surgery. It's just a far more difficult operation for the surgeon. But from the patient's perspective, there is a much higher risk involved in terms of side effects and negative consequences.

Is it in a man's best interest to find a surgeon who has done a lot of these salvage procedures?

Dr. Eastham: Yes. This is not something that is typically undertaken by someone who doesn't have much experience in terms of doing traditional radical prostatectomy. The surgeon needs a bit of experience and has hopefully been trained in dealing with post-radiation tissue changes.

Do you have any other advice for a man facing salvage radical prostatectomy?

Dr. Eastham: The issue is always: how curable is his cancer. The tendency after radiation therapy is to watch patients' PSAs rise for much longer than is clinically beneficial. The traditional definition of failure is the lowest PSA the man achieves plus two; this is called the Phoenix definition. Waiting for the PSA to rise two whole points just gives the cancer a chance to grow. But the earlier one treats prostate cancer, the better.

Waiting until the PSA is nadir plus two is too long for the patient to still be an optimal candidate for salvage treatment. The earlier the better. A man with a rising PSA after radiation, even if his PSA hasn't yet reached nadir plus two, should be considered for imaging studies and potentially a biopsy. Pp1

Charles Ryan, MD
Xtandi (enzalutamide) + Zytiga (abiraterone)

Dr. Charles J. Ryan is the Clinical Program Leader for Genitourinary Medical Oncology at the University of California, San Francisco Helen Diller Family Comprehensive Cancer Center.

He primarily treats men with advanced prostate cancer. His research focuses on novel therapies for advanced prostate cancer.

Prostatepedia spoke with him about Xtandi (enzalutamide), Zytiga (abiraterone), and the differences between the two drugs.

Why did you become a doctor?

Dr. Ryan: I grew up in a medium-sized city called Appleton, Wisconsin. My father was the first medical oncologist and the first prescriber of chemotherapy in our town. He never did a fellowship because they didn't exist when he finished his training.

I'm the youngest of four kids. By the time I was in junior high school, all of my siblings had gone away. My mother is a nurse, and she was working for hospice in our community. Sitting around the dinner table, it was just the three of us. The dinner conversation was frequently about cancer, hospice, medicine, and things like that. That's what shaped me at the time.

I decided to become a physician in college, but I had given a lot of thought to oncology and medicine well before making the decision.

I guess medicine is the family business?

Dr. Ryan: Yes. It is sort of a family business. When I started my medical training, I felt a kinship with the medical oncologists I interacted with at the University of Wisconsin. I was randomly assigned to work in an oncology clinic and a prostate cancer clinic. I just felt like: these are my people.

The timing was right for me to make a decision. It's what I wanted to do with my life. I found the disease itself biologically compelling, and the emergence of new therapies and the community of physicians and researchers who worked on it were an interesting group of people. It was a natural decision.

How do Xtandi (enzalutamide) and Zytiga (abiraterone) work? What are the differences between them?

Dr. Ryan: Xtandi (enzalutamide) and Zytiga (abiraterone) have been out on the market for a few years. They are both considered standard therapies in castration-resistant prostate cancer. The hormone receptor interaction is important throughout the progression and natural history of the disease. They are similar, but they are not identical in terms of their mechanism of action.

Zytiga (abiraterone) lowers the levels of androgens; it lowers the levels of testosterone and related molecules that are available for the cancer. Xtandi (enzalutamide) blocks the androgen receptor in a potent way. They both end up reducing hormone signaling in the disease.

Because they have different mechanisms of action, they have different side effects. The generic name of Xtandi is enzalutamide, similar to apalutamide (currently in development). They were invented in the same laboratory at University of California, Los Angeles.

Are they all used in the same set of patients?

Dr. Ryan: For the most part, yes. The initial approvals of the drugs for the disease were in patients with metastatic castration-resistant disease in post-chemotherapy patients (CRPC). Then there were two studies that tested Xtandi (enzalutamide) and Zytiga (abiraterone) respectively in chemotherapy-naïve CRPC patients. Both of those demonstrated a benefit over placebo in terms of delaying the disease, the onset of symptoms, improvements in survival, and a decline in functional status. Now they are standard of care for CRPC patients.

Recent reports of the LATITUDE and STAMPEDE studies done in Europe and Canada demonstrated that Zytiga (abiraterone) offers a survival benefit to patients when added to initial hormonal therapy, so that is a new standard for Zytiga (abiraterone).

Similar studies with Xtandi (enzalutamide) are ongoing and could demonstrate a similar result, which is to say, Xtandi (enzalutamide) could be used up-front in initial hormonal therapy.

That's a big change.

Dr. Ryan: That would be. Yes.

Are some men resistant to these therapies initially, or do they develop resistance? If so, is there any way of telling whether a man will be resistant?

Dr. Ryan: In terms of resistance to these therapies, it is fairly universal that patients will develop resistance to these therapies when they receive it in CRPC. Most CRPC tumors have mutations of one type, and some of them have many mutations that ultimately render them resistant to various therapies. One of the big challenges in the field over the last few years has been this question of whether these two drugs are so similar that we should simply choose one and use it, or whether we can use them in a serial fashion. In other words, we would treat a patient with Zytiga (abiraterone) until the disease becomes resistant, and then treat with Xtandi (enzalutamide).

Overall, the use of the second one of these is less effective. It's probably best to choose one and, if it's tolerated well, stick with it. When a patient becomes resistant to one of these drugs, using the other one may be of limited value.

There's no way to reverse or combat a man's resistance?

Dr. Ryan: It's actually quite complicated. In the laboratory, the androgen receptor and the factors that stimulate the androgen receptor are dynamic. It is possible that prostate cancer cells could become re-sensitized to these. There are some experimental suggestions that that could occur. However, we haven't really seen that bear out in the clinic. It's a rare patient who will develop progressive disease on Xtandi (enzalutamide) and then have a significant benefit to Zytiga (abiraterone), for example.

You touched briefly on combining drugs in this class with other types of therapy. Are there any others that appear more or less effective?

Dr. Ryan: The results of studies where Xtandi (enzalutamide) or Zytiga (abiraterone) were combined with other therapies are disappointing. At our center, we have tried to do a couple of these combination studies and have not seen results that would change the standard of care. We don't combine them with chemotherapy, typically.

There was a study that combined Zytiga (abiraterone) with Xofigo (radium-223); that study closed early due to excessive deaths and fractures. It looked like that combination may be dangerous. We're not sure why that is. Some more thought is going into that process.

There is a study underway that's maturing, which is a combination of Xtandi (enzalutamide) and Zytiga (abiraterone). We anticipate results in the coming year.

For the time being, these should be given as single agents, not in combination.

Has anybody looked at combining them with immunotherapeutic agents?

Dr. Ryan: The newer PD-1 inhibitor immunotherapies in prostate cancer are probably only active in a small proportion of patients with prostate cancer. And there are some studies underway with those, but no definitive data yet.

What's the experience of taking these medications like for patients? Are there severe side effects?

Dr. Ryan: With both of these drugs, there are patients who are at greater risk for side effects than others, so we need to think about the side effects, not for the whole population, but for individual subsets of patients.

There are a couple of side effects with Zytiga (abiraterone). Fluid overload, which is a function of salt retention, can be an issue for patients with congestive heart failure, edema, and those types of problems. Arrhythmias are associated with patients on Zytiga (abiraterone), but that may be a function of the fluid status of a patient. In other words, one of the side effects may be salt retention leading to fluid overload, which leads to arrhythmia. We don't see a direct cardiac toxicity with Zytiga (abiraterone).

Maybe 5-10% of patients on Zytiga (abiraterone) will develop liver function abnormalities and will probably need to stop the drug as a result of it. That could be really disappointing for some, and so

it underscores the importance of monitoring liver function in patients receiving the drug.

Because you have to dose Zytiga (abiraterone) with prednisone, that could be problematic for some, although the prednisone dose is generally quite low. Honestly, the main thing that's bothersome to my patients who take the low-dose prednisone is bruising on the skin, particularly on their forearms.

Xtandi (enzalutamide) is generally well tolerated. The major class of toxicities concerning with Xtandi (enzalutamide) have to do with the drug's ability to cross the blood-brain barrier, impairing some brain functions. But fatigue is the most common complaint we hear from patients on Xtandi (enzalutamide). That's probably due to a central nervous system penetration of the drug. When people were given high doses in early studies, there were seizures. We never see seizures in the current doses, but it is a theoretical risk and another sign that the drug can get into the brain.

Whether Xtandi (enzalutamide) has any effect on cognition, cognitive function, or coordination is currently being studied. There's a minor risk of falls associated with Xtandi (enzalutamide) therapy. There are some studies planned to look at more formal assessments of whether some patients experience cognitive problems on Xtandi (enzalutamide) and the risk factors.

Isn't Dr. Alicia Morgans working on that?

Dr. Ryan: Yes. Dr. Alicia Morgans and I are working on a protocol at Northwestern to look at the cognitive effects and the genetic risk factors for cognitive changes of Xtandi (enzalutamide). She's picked up on the testing methodology that would need to be done. Dr. Morgans has another study, which I'll participate in, that will look at both Xtandi (enzalutamide) and Zytiga (abiraterone) in terms of their effects on cognition. There will be other work planned in this area as well. Assessing cognition is not something most oncologists or urologists think about.

Is there anything that you could do to treat these cognitive deficits, or do patients just have to stop taking the drug?

Dr. Ryan: That's a great question because we're not sure whether cognitive deficits arise because of a preexisting risk and the drug accelerates that preexisting problem or if there's an issue specific to the drug. It could be a combination of the two.

If I see a patient who has a cognitive complaint on Xtandi (enzalutamide), I'll just stop the drug and put them on Zytiga (abiraterone), unless they've already had it. We don't know enough about this area or how to identify risk factors. Most patients do very well on these drugs without any cognitive changes.

Some patients or their spouse will complain about a cognitive problem during therapy, but there are probably people who have subclinical cognitive problems, and we don't know about them because we don't test them. That's that other area of work that we're looking forward to checking out.

Some people may not even be aware that they're experiencing those problems, right?

Dr. Ryan: That's right. Regardless of these therapies, many older patients have impaired cognition in general. It's not manifested unless they are studied or evaluated.

Do you have any advice or tips for men who have been prescribed either of these medications?

Dr. Ryan: Both of these medications offer significant clinical benefits. Either is a great opportunity for patients with CRPC to be treated beyond standard hormonal therapy.

I worked in some of the development of Zytiga (abiraterone), and we saw early on that only about two-thirds of CRPC patients ever went to a medical oncologist. Of that group, only about two-thirds ever received Taxotere (docetaxel). About 50% of the people out there who had CRPC were never getting any therapy beyond simple palliative treatments after ADT. That was one of the real opportunities for these drugs.

"The dinner conversation was frequently about cancer."

Now that they have been out for a while, they offer the opportunity for patients to take relatively well-tolerated treatments for a long period of time. They both extend life. And they're both associated with improvements to quality of life, so I think that's a critical benefit.

While we're not at the end of our knowledge on this pathway, we're no longer in the beginning stages. For example, we may see greater benefits with these therapies by using them before a prostatectomy, post-prostatectomy, in combination with standard hormonal therapy, or in combination with radiation therapy. It may be better to put some of our efforts to give this therapy earlier in the disease course.

You have a new book coming out in February from Benbella Publishing entitled The Virility Paradox: The Vast Influence of Testosterone on Our Bodies, Minds, and the World We Live In. *What led you to write this book?*

Dr. Ryan: As a medical oncologist who has treated hundreds of patients with prostate cancer with hormonal therapy, I became very intrigued by the reverse engineering of what hormone therapy does to patients. I wanted to explore what really happens to our patients when we deplete testosterone to treat their prostate cancer.

Many colleagues, trainees, and spouses of patients said that men became a lot nicer on hormone therapy. Men became better husbands. People joked about that, and after a while, I got to thinking that there's probably something to this.

I looked into the literature, and sure enough, studies that look at things like empathy found that the administration of testosterone to regular people can suppress or deplete our abilities to empathize and make moral decisions.

I dug a bit further and found that testosterone is implicated in a variety of conditions—not necessarily diseases, but conditions and decision-making. There's even some significant links to the amount of testosterone that we are exposed to before we are born and how that might affect our ability to learn words as babies. The diagnosis of autism may be driven by prenatal testosterone and a variety of other effects.

Then there's an interesting paradox. Testosterone can help preserve the brain and keep our brain healthy as we age. But on the other hand, we have patients who are losing their testosterone, and their spouses tell us they're becoming better husbands and nicer people.

There are at least two aspects of testosterone: the preserving aspect and the evolutionary aspect. The evolutionary aspect of testosterone brought us muscle strength for hunting, provisioning, breeding, and all the stuff that anthropologists say were important for the survival of our species.

This fascinates me because I treat patients with this disease, and we manipulate this really important hormone on a regular basis. Yet, our field has never really thought about the evolutionary and existential significance of the manipulation of testosterone. That's what got me started on the topic.

That sounds like a departure from the usual take on the testosterone. It seems like you're taking a broader view.

Dr. Ryan: Correct. Some say testosterone is all good while some say it's all bad. The truth is: it's both. We, who treat prostate cancer, are in this really unique position to observe people after the hormone that has basically defined their life is taken away. It's amazing to me that this alters some people but not others. For some men on hormone therapy, their testosterone goes down, and they say they feel better. Some say they don't think about sex as much as they used to, and that's freed up their brain for other things. Pp

Piet Ost, MD

Three or Fewer Prostate Cancer Metastases

Dr. Piet Ost is a radiation oncologist at Ghent University in Belgium. His work focuses on post-surgery radiation therapy and metastasis-directed therapy for oligometastatic prostate cancer, or a cancer recurrence with three or fewer metastases.

Prostatepedia spoke with him about treating men with so few metastases after treatment.

Why did you become a doctor?

Dr. Piet Ost: It was a bit by coincidence. I planned to be an airline pilot, but due to some medical issues with my eyes, I was not allowed to fly. I've always had a big interest in anything scientifically sound where you can start with science and build up from there. I found evidence-based medicine interesting from the beginning. So I started an alternate plan to become a doctor.

I enrolled in medical school and became more interested in getting patients involved in the science, in applying evidence-based medicine. How can we do that? Where are the big gaps in science?

In medical school, I realized that there are so many unanswered questions that patients ask on a daily basis. You just have to tell them what we know now, but that there are many things that we still do not know or fully understand. That communication process has helped me a lot in talking to patients. They helped me grow in this process once I graduated. It's an ever-learning process.

Can you define oligometastatic *prostate cancer?*

Dr. Ost: First of all, if your doctor talks about oligometastatic disease, I think it's very important to ask them what they mean by that? When we look through literature, there are several definitions used.

Some people use oligometastatic while others use oligo-recurrence, synchronous metastases, or low-volume metastases. Many of these probably mean the same, but there is no uniform definition.

In 1995, Hellman and Weichselbaum first defined oligometastases as metastases limited in number and location. These tumors have not developed the full capacity for metastatic growth. It could be an issue with the metastases—or the *seed*—or it could be an issue with the *soil*—the environment in which the metastases started to grow. That's the biological definition. This is not very useful as a clinician.

What is limited? Is that a certain number? If you look through literature, many clinicians define it as up to three metastatic lesions with no more than two different organs involved. That is probably the most used definition, but there are alternatives. Some say that it's only one metastasis while others say it's as many as five or even 10 in case of brain metastases. Some say there has to be a certain amount of time between primary diagnosis and the occurrence of metastasis. There's a lot of confusion throughout the literature. If you read an article, you have to look at their definition.

When doctors talk to each other, and when patients talk to each other, they all use the word oligometastatic, but it might be that they're talking about a different disease.

Is there any sort of restriction on where those metastases are located—for example, in only the pelvic area?

Dr. Ost: At this time, I don't think so. It's a biological phenotype. We care less where the metastasis occurs. For example, we have had patients with unique lung mets at the time of recurrence where we remove those lung mets, and then these patients remain disease-free for many months or even years.

"It might be that they're talking about a different disease."

Normally, when you have a patient with lung mets, those are visceral mets, and their prognosis is supposed to be very poor no matter what. There appears to be a subset of patients with a limited number of metastases, even visceral metastases, who still benefit from removing or irradiating the metastases. We have several of those cases documented already. It's not about the location. It's something about the biology, and that is the big problem at this time.

Currently, when we propose a certain oligometastatic or metastasis-directed therapy to a patient, we don't know if the metastases we see and treat are the only ones there, or if three months after we remove or eradiate them, there will be 20 new metastases. We don't know that at the start. This shows us that imaging is still far from perfect and sometimes we only see the tip of the iceberg.

When we look at the distribution or pattern of metastases in recurrent prostate cancer with Choline PET/CT and PSMA PET/CT imaging, we see that, after receiving prior prostate cancer treatment, the majority of patients relapse first in the lymph nodes. That is mainly in the pelvic lymph nodes. If we look at all the patients that we screen for now, 70% have nodal recurrences, 25% have bone metastases, and 5% have visceral mets. If we look at all of those recurrences, two thirds of those relapses are what we call oligometastatic, meaning up to three metastatic spots.

We don't believe that there is a true limitation on the organs. How it evolves is actually a fingerprint of the disease. When you start, you don't know whether it's a true oligomet. We cannot predict at this time how the disease will evolve.

How do you normally treat oligomets? With radiation or surgery? How do you decide which is most appropriate?

Dr. Ost: We still counsel our patients on the standard options. For patients with upfront metastatic disease, the landscape has changed dramatically where we now introduce Androgen Deprivation Therapy (ADT) plus Taxotere (docetaxel) or ADT plus Zytiga (abiraterone) as a standard of care. We still do not know if these options are helpful in treating the primary tumor and its mets with metastatic-directed therapy.

In situations with upfront oligometastatic disease, we counsel our patients that the standard of care is systemic drugs while the addition of any metastatic-directed therapy is one big question mark. We do not advise it outside clinical trial.

The situation is a bit different in the recurrent setting. In the recurrent setting, there's a gray zone. For example, the older data said that starting ADT for a PSA relapse following primary therapies—just starting ADT—is not advised; it's better to *wait and see* and do a delayed ADT at the time of symptomatic progression.

Now with the very sensitive imaging, we see mets earlier at PSA relapse. What should we do with these? Do we still say the standard of care is *wait and see*, ADT, or something else?

Because new imaging created this gray zone, all of a sudden we saw a boom in these oligometastatic patients, so we decided to do a clinical trial in this setting.

In our paper published in *The Journal of Clinical Oncology* (JCO), we randomized our patients to *wait and see*. One group had surveillance while starting ADT, and the other group had surgery or radiotherapy to the mets followed by surveillance. In that study, we found that surgery or radiotherapy is better at postponing further progression to polymetastatic disease rather than just observing patients.

We have an alternative now in counseling patients: metastatic-directed therapy with either surgery or radiotherapy. We know that it's very safe, because we did not see any grade 2 or higher toxicity, which is a positive thing to tell men with prostate cancer. We can offer you something without a whole lot of toxicity. We still have to tell you this was a Phase II trial. The endpoint was time to progression.

I'm still not sure that giving metastatic-directed therapy will change your disease in the long run, that it will make you live any longer compared with immediate ADT or surveillance. It's still too early to tell. We try to counsel our patients with these different options.

What are the side effects like after those types of treatments? If someone's had radiation, and he recurs with oligometastatic disease after that, will more radiation be more problematic because of scarring from the original radiation?

Dr. Ost: The answer is actually no. We've treated the primary prostate and we rule out the local recurrence. Typically, we see oligometastatic recurrences outside our previous radiotherapy field. It depends on the location.

"We cannot predict at this time how the disease will evolve."

For example, if you see a pelvic nodal recurrence and that patient never had surgery in the pelvis, we counsel them on their different options. We can do a salvage lymph node dissection, taking out the suspicious node. We can do a complete template resection, which means removal of all the other nodal changes in those areas of the pelvis. Or we can just go for stereotactic body radiation therapy (SBRT) to that suspicious node. Of course, if you ask us which is best, the answer is we don't know. There is a difference in side effects.

If we do an SBRT to a few nodes, we rarely see any toxicity. We never see any grade 2 or grade 3 toxicities. We see only grade 1 toxicity, which means some mild bowel discomfort during one or two weeks. Even that is very rare. We only see that in one out of ten patients. It's quite rare to see any side effects with SBRT for prostate cancer to the small volume metastases.

The situation is a bit different with salvage lymph node dissection. There you need surgery, so you will have to go under general anesthesia. There will be some time to recover. Normally, you will have some potential postoperative complications, such as some lymph node and wound leakage, as well as wound healing issues. There are other small complications, but the more severe complications are infection or wound dehiscence (where the suture didn't hold), and these require intervention. Serious lymphedema has been reported as well. We don't see these with SBRT.

We counsel our patients on the advantages and disadvantages of both approaches. If they want to know which approach is oncologically best, we still don't know. That is actually the subject of a trial that we will launch in Europe to find out which is the best option.

When will that trial open?

Dr. Ost: We hope to open in the next two months in Belgium, Switzerland, and Italy. We are ready to submit to the ethical committee.

If anybody reading this is interested in participating, should he contact you?

Dr. Ost: They can contact me. We can see if there are centers in other countries willing to join. It might be very likely that there are alternatives in the United States as well because there are some very nice trials running there.

Patients from Australia or the United Kingdom might be interested the United Kingdom-led CORE trial. The CORE trial randomizes patients between standard-of-care and standard-of-care plus SBRT after oligometastases. It's already open for patients.

If men are treated for oligomets, rather than doing surveillance, are there any implications for further treatments down the line? Does it preclude them from getting another kind of treatment if the metastases become more widespread?

Dr. Ost: No, at this time not really. We keep the ADT as a reserve until actual progression. We still see that ADT works the way it should work. There's no real indication that certain therapies or certain drugs might work or are less likely to work when you receive SBRT, salvage surgery, or whatever. We don't hamper any future treatments at all.

Any other thoughts or advice for men who are facing this type of situation and are either not sure what to do or their doctor doesn't really know what to do either?

Dr. Ost: It's very important to have an open discussion with your physician and try to find the available evidence out there. Evidence is starting to pile up that metastatic-directed therapy is best for patients with up to three metastatic deposits. For those patients who may want an alternative to ADT, metastatic-directed therapy might be a very good option. I would still prefer them to join a clinical trial, because there are still no long-term results. At this time, metastatic-directed therapy should still be looked at as an investigational treatment.

As you said, there are number of trials that patients can join.

Dr. Ost: Especially in the United States, there is a boom in clinical trials. For example, for patients who have a primary tumor in place and limited mets, there is now a oligomets trial open that is led by Brian Chapin. This SWOG trial will compare the standard of care with standard of care plus treating the primary and the metastases. For patients with recurrent prostate cancer, the ORIOLE trial led by Dr. Phuoc T. Tran at Johns Hopkins is of interest.

There are a variety of options for American patients who would like to join a clinical trial. These trials can be found at clinicaltrials.gov. Pp

Clinical Trial: 18F-DCFPyL PET/CT in Recurrent and High-risk Prostate Cancer

Dr. Peter Choyke, Director of the Molecular Imaging Program at the National Institutes of Health's National Cancer Institute, is keenly interested in translating molecular imaging methods like MRI and PET into practice.

Prostatepedia spoke with him about his clinical trial on 18F-DCFPyL PET/CT imaging in high-risk prostate cancer.

Why did you become a doctor?

Dr. Peter Choyke: I was always interested in science. I came from a family of scientists. It just seemed that medical problems were the kind of problems that I needed to do work on. A lot of the problems in physics and chemistry had been solved, but in biology and medicine we really needed a lot more effort. I wanted to devote my life to that.

Can you explain the thinking behind your clinical trial on 18F-DCFPyL PET/CT imaging in high-risk prostate cancer?

Dr. Choyke: Prostate cancer imaging has been very limited. We've only had access to CT and bone scans, both of which had limited sensitivity for picking up prostate cancer. In the beginning of the 2000s, a number of new PET agents—or Positron-emission tomography labeled agents—emerged. We started looking at them as they became available. They showed better and better sensitivity and specificity.

About three or four years ago, we accessed a first generation PSMA-targeted PET agent named F-18 DCFBC in collaboration with the person who invented this whole field, Dr. Martin Pomper at Johns Hopkins University.

We formed a collaboration and scanned 135 patients in an earlier protocol. We showed that even though this was a first generation PSMA agent, it was really promising and had much better sensitivity and specificity for prostate cancer than any other agent we had ever looked at.

Then Dr. Pomper, who is partly an imaging specialist and partly a chemist, further developed the compound into F-18 DCFPYL. This is the agent we're now using in this trial.

F-18 DCFPYL has probably 10 times better sensitivity than the first-generation agent because of the higher affinity of the agent for PSMA and because of lower background. We started using that in the end of the summer of 2017 in a trial looking at high-risk primary cancer and recurrent disease.

If a man enrolls in this trial, what can he expect to happen from beginning to end?

Dr. Choyke: First of all, it's important to talk about who qualifies for the trial. We have two arms.

In one arm, we'll have men with high-risk cancers, meaning they're at high risk for metastatic disease or spread outside the prostate. Such men would come to our center and get the scan. They'd also get an MRI of their prostate, because we always correlate the findings of the DCFPyL scan with MRI to anatomically locate where the uptake is occurring. The anatomy is very complex in the low pelvis.

With the MRI in hand, the patient would get an injection of a small amount of radioactivity in the form of this F-18 DCFPyL. About an hour later, they go onto the scanner and simply lie flat for about 20 to 30 minutes until the entire body is scanned from head to toe. Then we'll report the findings back to his physician.

Part of the reason why this is a research study is that we try very hard to correlate the findings that we see with biopsy specimens. This is still a research agent. We don't know for sure that the areas of uptake are actually cancer. We can only confirm that

"Prostate cancer imaging has been very limited."

with biopsy. We insist that patients undergo biopsy of PSMA-positive lesions as seen on the scan.

We say insist, though of course it may not be medically safe for some people to undergo a biopsy. It may not be feasible. There are exceptions. It's not an absolute rule. We certainly want to get as much histologic correlation as possible. Otherwise, we could end up in a situation where we think we're seeing disease, but we are in fact not. That would be very misleading and could possibly cause more harm than good. It's very important at this stage of development to get as much information as possible.

In the second arm of this trial, we are scanning patients who have already undergone radical proctectomy or radiation therapy and who now have a rising PSA, which indicates recurrent disease. We would do the scan in the same way as in the first arm with correlation of the MRI. Again, we're trying to get as much histologic confirmation as possible.

Do patients need to come to you to get the scan done, or are there other locations besides the National Institutes of Health (NIH) in Maryland?

Dr. Choyke: The way this study is set up, it is only being performed at NIH.

Is there an associated fee for patients?

Dr, Choyke: That is a good question. The NIH is set up in a way that there are no fees for patients. The patient may need to spend some money to travel to Bethesda, Maryland, but all the medical care that they receive, including the experimental scans, are without cost.

Does the scan require a one-day visit?

Dr. Choyke: Because there is an MRI involved as well, it may entail two days in some cases because of scheduling issues. It can often be done in one day.

"It was really promising."

Is there anything else that you think patients should know about the study itself, or the logistics of participation?

Dr. Choyke: This is an experimental study. We have already seen patients who assume that this is a proven entity. They think that whatever the results of the scan, that's what they have. But in fact, this is a research study for the very reason that we don't know all those things. You have to make informed decisions with your physician about the results of these scans and not automatically assume that the scans are telling you exactly what is going on. In other words, an informed discussion about the results is important.

I must also say that this is a very popular protocol. We do have a backlog. Fortunately, prostate cancer is not usually a rapidly progressing disease. A several week delay in getting your scheduled appointment is not catastrophic for most patients. That's just one of the problems of having a limited source of the agent. We have to make each dose ourselves. There is no

"This is still a research agent."

company behind this. This is a handcrafted procedure.

How many patients are you going to enroll, and how many have you already seen?

Dr. Choyke: We're enrolling 225 patients in this protocol. We have already seen 40. We're just at the beginning.

We have a companion protocol for patients with metastatic disease that will accrue 100 patients. That trial is for patients who already have metastatic disease and we're looking for an improved assessment of the status of their disease. It's a very exciting protocol in that we will understand the strengths and limitations of PSMA scanning a little bit better in the metastatic disease setting—where the disease is much more varied than in the earlier phases. Pp1

How To Get Involved…

For more information, email Dr. Peter Choyke at pchoyke@mail.nih.gov or calling 301-402-8409

Patients Speak
Maurice: My Prostate Cancer Story

Maurice W. was in his 80s when he found out he had prostate cancer.

He spoke with *Prostatepedia* about his journey.

How did you find out that you had prostate cancer?

Maurice: I had bladder cancer about five or six years ago. I started having some serious pain, what the doctor called bladder spasms. I was having trouble urinating and frequently urinating at nighttime. It was so painful at times that it was even causing hemorrhoids, because I was straining to urinate.

I called the urologist and mentioned I was having all of these problems. He said, let me put a catheter in. I went in on a Friday; his nurse put in a catheter. It felt a little bit uncomfortable the next day, so I called his office. He said I'm on my way home, so I'll stop by and check the catheter. He came by and he put a new catheter in. He said while I'm here let me check your prostate. He did a digital exam and said I think we better get you in on Monday for a CAT scan. That is where we found out that things were not normal.

Then, of course, we did the PSA test. My PSA was 413. I hadn't had a PSA test for about five or six years. When I gave my primary care physician the numbers, he said something must be wrong. But it had gone from 4.4 to 413 six years later. That is how it really started.

What was going through your mind at that time?

Maurice: After all these years of pain with the urination, I thought, well at least I know what's wrong. I wasn't really shocked. The idea of cancer wasn't new, since I had had bladder cancer about five years before. The shock came afterwards. I started asking myself why did I let it go that long before I got checked? It was more self-examination than shock. I was starting to look at myself and asking why wasn't I more proactive?

With prostate cancer, I just went along with the protocol. You don't do anything after a certain number of years and it can be treated as a mild, chronic disease. They give you that story. So you're just going along with the general thinking.

I really wasn't that shocked, to tell you the truth. It was good to know what was going on. The urologists and the oncologists said we've got lots of good options here, so don't get too panicky.

In that initial phase after you found out you had prostate cancer and before you decided on a treatment, what did you do? Did you just talk to your doctor? Did you talk to family and friends?

Maurice: I talked to my primary care physician first. He found me an excellent oncologist. He came highly recommended. He even went to school with my wife's niece's husband, an oncologist who wrote a Pulitzer Nobel Prize winning book called *The Emperor of All Maladies*.

You talked to him?

Maurice: That's my wife's niece's husband. He knew my oncologist because they both trained at Dana Farber Cancer Institute.

Did you talk to Siddhartha Mukherjee about the kinds of recommendations your doctor was making?

Maurice: No, but his father-in-law (my wife's brother) spoke to him and he agreed that what they are doing for me is the best treatment.

What types of treatments did you have?

Maurice: The first one was Lupron (leuprolide). The Lupron (leuprolide) looked like it was doing some good. My PSA dropped from 400 to about 11 during the first three months.

The doctor got a little bit impatient. He said we're going to do the next phase with Zytiga (abiraterone). The Zytiga (abiraterone) kicked in about six months later. My PSA has been going down regularly over the last four or five months. It's been effective. I don't seem to have any side effects. That's a good sign. As of December 2nd, my PSA is down to 0.20, which is really quite dramatic. I'm very pleased.

What kind of imaging have you had?

Maurice: The first bone scan showed a horrible image—black stuff all over my rib cage and my pelvis. They did another one two or three months ago. I can't interpret the images, but they said there has been a vast improvement because of the medication. To my untrained eye the second imaging looks pretty good.

I suspect at my next visit, they might want to do a bone density test to see the effect of the new bone -strengthening medication. For my age, it's miraculous. My family doesn't want me to drive in case I have a car accident—the risk to my bones.

I had to have a partial hip replacement because of a fracture of the upper femur in the left leg from metastasis. It's very limiting when you have something like this. You're already limited by age. Then having this thing thrown in on top of it. It's not good. I'm hoping that I can carry on with my life as normally as possible. My children don't want me to drive any more.

What do you do when you need to go somewhere? Just wait until a family member can drive you?

Maurice: Right now, I'm still driving.

Oh, but they don't want you to drive.

Maurice: Yes. My daughter-in-law is very good. She tries to pitch in. But if I have a short errand a few short miles from here, I'm not going to handicap myself because the chance of having an accident is pretty small. I'll take the chance. My attitude is that your whole life is chance anyway. I could get in an accident in a taxi cab or an Uber or in a friend's car.

You can't eliminate all problems in life. But children are what they are. They want to look after their parents.

It comes from a place of love.

Maurice: Right.

What is the plan going forward for your prostate cancer?

Maurice: They're concentrating on my bones right now. I am now getting Xgeva (denosumab) to promote absorption of calcium into the bones. It looks like we've got the PSA under control. They want my PSA as close to zero as possible, so they're going to keep me on the Zytiga (abiraterone). It's doing the job, so they're going to keep me on it. But the question in my mind is: what happens if the Zytiga (abiraterone) decides it's not going to be effective anymore?

All these things come to mind. You can't help but think about them. I was very casual about things, but now with the support group that I belong to, everything gets wound up to a higher level.

How did you find your support group?

Maurice: I have a good friend who had his prostate removed. His PSA was much lower than mine. His Gleason number indicated that he was going to have a problem. I think he's 80 now. He was about 70 when he got his prostate removed.

His wife is really an activist. All the doctors said no, you're too old to have your prostate removed. But she's quite medically savvy. She does all the research. She made sure they removed his cancer.

He's fine now. He's the one who got me interested in the support group. He's very kind. Every month, he gives me a ride to the meeting. We have dinner.

About 10 to 15 people show up every month. They're all in different stages of prostate cancer. Some people are very young. Of course, they don't want Lupron (leuprolide) because that restricts their sexual activity. They're trying to balance two things. It's an eye-opener for me.

I'm the oldest one. I'm also the one with the most unusual type of cancer. Most of them caught their cancer earlier. They've been treating it for a while.

I'm the one who got caught in this statistical web. I heard this definition for a statistician: he's like a blind man holding on to a lamp post for support but not for illumination. In other words, he's hanging on for dear life, but he's not really enlightening anybody. You know statistically I'm not supposed to have what I have. I'm one of those crazy things that just happens. My urologist said I'm just an outlier. That doesn't make me feel any better, but that's what I am.

Do you have any thoughts for men in a similar situation?

Maurice: People should continue getting their PSA checked even when they get into their ripe old age. You can still get this thing at an old age. You still want to detect it as early as you can. If I had detected mine two or three years earlier, I wouldn't have my bones metastases. You still want to catch the thing as early as possible.

It's fine for the doctors to say we'll treat prostate cancer as a chronic disease, but it's ruined my quality of life. It's a detriment. It reduces my quality of life considerably, even though the oncologists are very happy that their treatment is working. Why not? That's what

they are trained to do. But it's the man who pays the price.

I think the doctors have to take a better look. People are living longer. They keep saying, "At your age, don't worry about it. You're going to die of something else." I don't think that's true anymore. People are living longer, and they need to be treated differently. They should not just barely tolerate us but treat us as normal human beings with a life.

They shouldn't say, oh you only have a few years left. Because you never really know when you're going to go. You don't know when you're going to die.

You may live to be 100.

Maurice: I live in this retirement place. There are lots of people around here in their 100s. Doctors should be more aware. These are people. They're not just statistics.

Doctors definitely need to reassess how they look at PSA testing. Don't stop looking at PSA after a certain age. Maybe check it every two years. Not every year. But certainly keep an eye on it. Their guidelines are outdated.

Everybody's life is valuable. Each person is an individual with feelings. The only thing that I regret is that I wasn't more proactive when I was having all these problems. I should have been more aware that something was not right.

A lot of people do that. We all tend to ignore injuries or illnesses until they become something we can't ignore.

Maurice: I think you're right. Most of us don't complain. We put up with it. You don't want to be a nuisance, but there's a happy medium. Pp

Jamie Bearse: Dealing With Recurrence

Mr. Jamie Bearse is the CEO of ZERO — The End of Prostate Cancer (www.zerocancer.org). ZERO is a United States-based nonprofit with a mission to end prostate cancer.

He talks to *Prostatepedia* about dealing with recurrence.

Finishing your prostate cancer treatment is cause for celebration and relief. Life is best lived in the moment as we all only have today. However, stress about side effects and thoughts of recurrence creep in. It's critical not to live in an anxious world of *what if*, but it's important to know that up to 40 percent of men will experience a recurrence after completing treatment. For those who do experience recurrence—whether it is biochemical or metastatic disease—we'd like to share some tips for coping with the journey ahead.

Talk to your doctor about every aspect of your new diagnosis, including your treatment options.
It's important to understand whether you are experiencing biochemical recurrence or if your cancer has become metastatic and what your treatment options are. At your appointment, take detailed notes, or bring someone with you to do so. Afterward, do your own research about what you discussed with your doctor, and if you still feel unsure, seek a second opinion. Much like when you were first diagnosed, it's important to understand all options available to you based on your specific disease and circumstances.

Consider joining a support group.
Support groups offer the chance to share feelings and fears with others who understand, as well as to exchange practical information and helpful suggestions. Connecting with other men whose cancer journey is similar to yours can allow you to explore options and seek advice from someone who has been there before.

Try to lean on your loved ones.
Your loved ones want to help you through this newest obstacle – try not to be afraid to open up and talk about how you're feeling. If you don't feel comfortable talking to someone, write down your thoughts in a journal. Talking and thinking about your concerns as you work through your options can help you feel less afraid or anxious and more in control.

Utilize all resources available to you.
If you don't feel comfortable talking to a loved one or a support group, or if you feel you need additional support, consider calling ZERO360 at 1-844-244-1309 Toll-Free, a free one-on-one patient support service that can help you find qualified counselors and emotional support resources.

The fear of recurrence is normal and reasonable for all cancer survivors. Although you cannot control whether your cancer recurs, you can control how you move into this next phase of your prostate cancer journey.

ZERO also offers a new, peer-to-peer MENtor program, which can match you with a patient or survivor who has experienced a similar diagnosis or treatment pathway for one-on-one support. In addition, if you're experiencing recurrence and are looking for additional resources to help, visit www.zerocancer.org/get-support/zero360. Pp

MAP YOUR PATH FORWARD

WITH ADVANCED PROSTATE CANCER

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

UNDERSTANDING YOUR ROAD

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

CHOOSING YOUR ROAD

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

FINDING YOUR WAY

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

VIEWPOINTS FROM THE ROAD

Educate and empower yourself with educational articles and real stories about people facing prostate cancer.

Visit www.MyProstateCancerRoadmap.com/start to stay in the know and subscribe to our newsletter.

Janssen Oncology

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

Coming Up!

April:
Genomics + Prostate Cancer

May:
Joining Clinical Trials

June:
Collaborations