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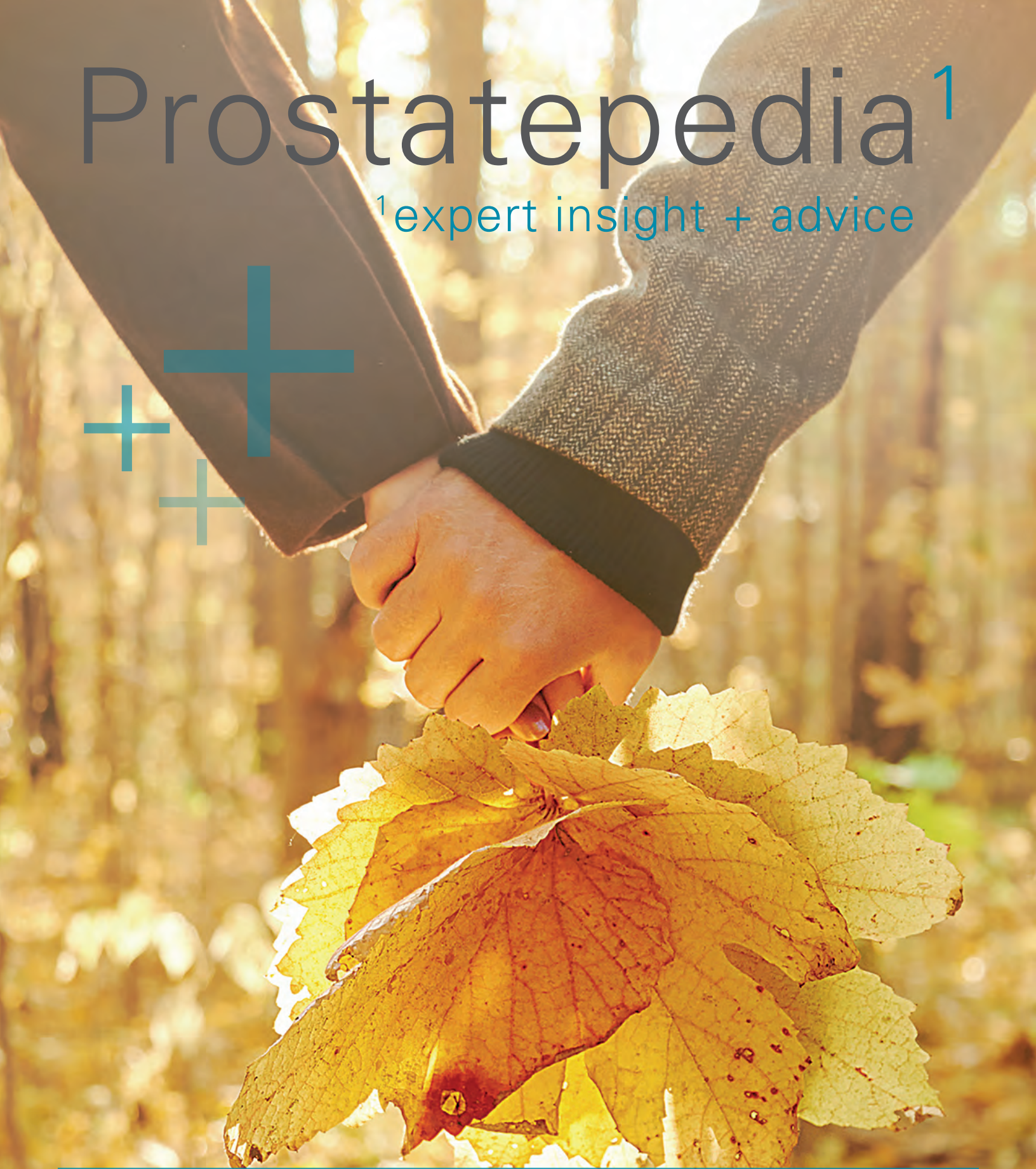

Advances in Imaging

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In this issue....

In October, we're discussing advances in imaging that could dramatically improve how we treat prostate cancer. In our Guest Commentary, Dr. Neal Shore does an excellent job summarizing these advances from a urological perspective, expanding on the interviews by Drs. Matthew Cooperberg and Raoul Concepcion. Dr. Michael Zelefsky discusses the impact these new imaging approaches, especially MRI, have in prostate cancer treatment planning.

Several common themes emerge. One is that the American healthcare system renders the best imaging technologies so expensive that rapid implementation at the community level is limited. The situation in Europe is markedly different; costs are 70-80% lower. As a result, Europe is leading both the development of better imaging technologies and the delivery of these technologies at a community level.

Another common theme is that advanced training and experience are required to use these imaging technologies well. Dr. Cooperberg does an excellent job of outlining this problem in prostate multiparameter MRI. The message for you is just because a nearby medical facility has purchased state-of-the-art imaging equipment does not mean they know how to use that equipment well. For now, travel to centers with a documented track record in using a new imaging technology.

Perhaps the most important point is that before a new imaging technology becomes standard treatment, extensive clinical trials need to validate the technique. How do you know when an imaging technique has passed such scrutiny? One landmark is whether or not the imaging technology has been FDA approved. For example, the C-11 Choline and Axumin imaging scans are FDA approved and covered by Medicare to detect metastatic prostate cancer. The Gallium-68 PSMA PET/CT scan is very promising, but not yet FDA approved.

In several of this month's conversations, we mention the role of imaging in the management of oligometastatic disease. In oligometastatic disease treatment, we use radiation or surgery to eliminate metastases, potentially delaying cancer's progression for a clinically useful time. By now, it is clear that there are patients who benefit from this treatment. What is not clear is how effective we are at identifying who those patients are. This will only be resolved by well-designed randomized clinical trials. Fortunately, such trials are in progress and additional trials planned.

Charles E. Myers, Jr., MD

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Guest Commentary
Neal Shore, MD

Imaging is important for newly diagnosed prostate cancer patients who may or may not have localized disease, and it's especially important for advanced prostate cancer patients, whether they continue to be androgen sensitive or have developed some level of androgen resistance. For earlier stages of disease, there has been a lot of interest regarding multiparametric MRI. Nonetheless, the efficacy of multiparametric MRI is limited by the expertise of the interpreting radiologist. The fusion technology software championed by several of the academic centers has been rolled out without consistency within the community. For some practices, it was adopted due to marketplace competition and the device developers' promotions. Companies that develop multiparametric fusion technology have not made a significant contribution to the advancement of urologic and radiologic educational needs. That said, some groups incorporated dedicated specialists within their practice to train for high-quality multiparametric fusion-based biopsies. Purchasing the newest promising technology without ensuring a framework to optimize clinical results will lead to poor implementation.

In the United States, MRI is still mostly recommended for patients who have had a negative prostate biopsy, but due to age, PSA kinetics, or rectal examination, there is still a concern of possible malignant disease that was missed on the first biopsy. MRI is most uniformly accepted for additional information when evaluating patients for the need for a second biopsy. MRI will no doubt have an ongoing role in the active surveillance population. MRI will no doubt have an eventual role in decision making for possible first biopsies.

There has been a lot of very good, evidence-based literature coming from European countries that suggests that whole-body MRI, with the right software protocol, is exceptionally helpful in evaluating metastatic disease. Unfortunately, in the United States, this protocol takes 45 to 60 minutes to accomplish, and unfortunately, translates to a challenging economic utility model for the MRI efficiency from an administrator perspective. There are many interesting and promising blood-, tissue, and urine-based markers, genomic assays, and additional imaging techniques, which require ongoing trials to determine how best to use them for the most efficient value-based care model.

No single test—MRI or any other blood-, tissue-, or urine-based marker —is perfect. Eventually, we will hopefully develop a cost-effective algorithm that combines a panel of all the different biomarkers. MRI is part of that discussion, but we don't have that sorted out currently.

There have been multiple PET scan technologies developed in the last several years that have been assessed for improved potential sensitivity and specificity, and ultimately, to improve the accuracy of the data that shows cancer spread and its location. MRI and Axumin PET scans have been approved for advanced prostate cancer patients. There have been other PET scans such as FDG, C-11 Acetate, C-11 Choline, sodium fluoride, which have not received widespread reimbursement approvals nor widespread accessibility. There is also no consensus recommendation for these technologies. Pp[1]

Matthew Cooperberg, MD

Imaging: Diagnosis + Staging

Dr. Matthew Cooperberg is an Associate Professor of Urology and the Helen Diller Family Chair in Urology at the University of California, San Francisco. He is keenly interested in risk-stratifying prostate cancer to better match treatments to those most likely to benefit.

Prostatepedia spoke with Dr. Cooperberg recently about how advances in imaging have impacted how we diagnose and stage prostate cancer.

Why did you become a doctor?

Dr. Cooperberg: I have a math and science mind, but I have always been drawn to the liberal arts, too. I was an English major, and I also studied history and art history in college. What drew me to medicine was that it is incredibly stimulating intellectually, but also has a lot of human contact—and human challenges—as well as scientific ones.

How have advances in imaging improved our ability to accurately diagnose and stage prostate cancer?

Dr. Cooperberg: Imaging plays an emerging role. We have to be careful in this field—and specifically in this place in history—not to confuse advances in research with advances in clinical care. There are lots of exciting things going on with imaging research in prostate cancer that are presented to patients as being ready for prime time, but they are not ready yet in most community settings.

Two major imaging stories are evolving right now. One is better local assessment of the prostate itself, mostly based on MRI. The other is better staging with advanced imaging modalities centering on PET/CT, specifically prostate-specific membrane antigen (PSMA) PET/CT imaging.

"Two major imaging stories are evolving right now."

MRI imaging of the prostate has been a little bit of a challenge. Prostate cancers are notoriously not visible on CT scan and are only marginally visible on the historical MRIs that would be done in single phase, primarily to image the lymph nodes.

Ultrasound, which is what we use to guide prostate biopsies, can identify a reasonably high proportion of prostate cancers, especially high-risk prostate cancers. However, doing ultrasound well takes a lot of experience and expertise. There are urologists who use ultrasound to identify the different regions of the prostate and don't spend that much time looking for the cancers. With practice, it is possible to see at least a significant proportion of cancers with ultrasound.

In the last few years, the goal with MRI is to do a better job with local assessment of prostate cancers. Can we see the cancers? Can we accurately stage them using a multiparametric MRI exam? That means looking at T2-weighted imaging, which is essentially anatomic imaging. We look at diffusion weighting, which is intended to give an indication of cellular density. And we look at dynamic contrast, which gives us a sense of how much angiogenesis is going on. That combination of imaging modalities all within a given MRI exam definitely gives us a lot more information than before. The goal is to see the tumor within the prostate and to get a measure of its stage. However, this all depends on accuracy, which remains highly variable.

The UK has been a major proponent of MRI for a long time. Most reports suggest that there is improved accuracy when you do an MRI biopsy versus an ultrasound-guided biopsy. This means that we miss fewer high-grade cancers.

The problem with a traditional biopsy has always been both under-sampling and over-sampling. You find small Gleason 3+3 prostate cancers that you do not need to find, and there is a chance of missing higher-grade cancers.

With MRI, both the overdiagnosis problem and the underdiagnosis problem tend to improve. Most agree that an MRI can identify cancers that would be missed on the ultrasound. Whether MRI can replace the standard mapped-out biopsy is more controversial.

In places like the UK, they are on the cusp of implementing a policy in which patients with an elevated PSA get an MRI-targeted biopsy if the MRI shows something. If the MRI doesn't show anything, you don't get a biopsy. But I don't think the world is nearly ready for that. Even in the best series, there is quite a substantial risk of under-sampling with MRI-targeted biopsy alone. It is common to find higher-grade cancer with the non-MRI-guided biopsy.

The bigger problem, moreover, which is barely discussed, is with observer variability in reading the multiparametric MRI. A CT scan of the kidneys, for example, is a very consistent, straightforward test. Pretty much any radiology center can push "start" on the CT scan and generate similar-looking pictures. Any half-decent radiologist should be able to read the CT scan of the kidneys.

A multiparametric MRI of the prostate is a completely different story. There's a lot of subtlety and a lot of expertise required in programming the machine, protocoling the exam, and interpreting the results.

We see patients who had a prostate MRI at an outside radiology center that is completely unreadable: it hasn't been performed correctly, let alone interpreted correctly. Even if it is done right, there is an observer variability problem.

"A community radiologist who looks at one prostate MRI a month is not going interpret as well as a radiologist who reads them frequently."

There have been studies in places like the National Cancer Institute (NCI), who are major experts at MRI, but even at the NCI, there is major interobserver variation because there are shades of gray in terms of how we identify these lesions. (Observer variability is the failure to read the test accurately; interobserver variability refers to two or more clinicians interpreting different results from the same test.)

Would you say that MRI-guided biopsy plus the traditional biopsy would be a better approach?

Dr. Cooperberg: Because of the interobserver variability problem, I don't think we should be anywhere close to getting rid of the traditional biopsy—not even in a center of excellence like NCI, and certainly not in a community radiology setting. Also, the sensitivity of MRI for high-grade cancer is still not as high as we'd like it to be.

There are lots of other questions. How do you do an MRI-targeted biopsy? Do you do what is called cognitive fusion, meaning you just review the MRI to guide your ultrasound-guided biopsy? Do you use fusion systems where we overlay the MRI images onto the ultrasound picture at the time of biopsy? Or are we doing an in-bore MRI-guided biopsy where the biopsy is done under direct MRI guidance in real time? These latter options increase complexity and cost. There is minimal evidence that one is particularly better than another.

Plus, the better you are at identifying lesions by ultrasound, the less commonly you are going to miss something on ultrasound that you would have seen on MRI. We do a lot of MRI at UCSF. We're a big MRI center, and I order MRIs all the time because we have subspecialty radiology expertise available. A community radiologist who looks at one prostate MRI a month is not going interpret as well as a radiologist who reads them frequently.

Should patients ensure they get their MRI done at a center of excellence?

Dr. Cooperberg: Absolutely.

What are some of the obstacles to eliminating this interobserver variation? Education and training?

Dr. Cooperberg: That's part of it.

We've got the usual problems with reimbursement. Using these outside centers as an example: they frequently do a poor job, but they still get full reimbursement for the MRI. MRI is priced higher in this country than in most places in the world. Part of the reason MRI has become so common in the UK and in most of Western Europe is that it only costs a few hundred dollars there. Here, the charges run into the thousands.

Why such a big difference?

Dr. Cooperberg: The American healthcare system. We overpay outrageously for imaging compared to the developed world.

Could an American patient travel to the UK to get an MRI?

Dr. Cooperberg: They could, although I'm not sure what it would cost them if they're out of the National Health Service (NHS) system. It costs the NHS a few hundred dollars because they're just providing the care. You don't have this absurd mismatch across cost/charge/collection that we have in the US. In the US, there is the cost to the hospital—amortizing the machine, the electricity, running the magnet—what they charge the patient, and what they collect from the insurance company. Those numbers have absolutely no relation to each other. Because it's a single-payer system in the UK, there's only one cost to the system.

The UK also has a private system. I don't know what the cost is for a private patient in the UK, although I think it's still in the hundreds of dollars, not in the thousands. In Australia, which has universal coverage as well as a pretty big private sector, I believe it's also a few hundred dollars.

So given the costs and complications, are you saying we should not standardize combining traditional biopsy with MRI-guided biopsy? That we should save this MRI-ultrasound fusion for an unusual diagnosis?

Dr. Cooperberg: I don't think every patient needs to have an MRI either before or after a biopsy. MRI should be done selectively, when appropriate.

There are specific instances when it can be helpful. If you have a standard biopsy that shows high-grade prostate cancer, you will probably need treatment. I'm not sure how much additional information the MRI will give you at that point. One of the tenets should always be: never order tests if the results won't change the management.

What about MRI for men on active surveillance?

Dr. Cooperberg: For me, two areas of biggest interest are patients who have not yet had a diagnosis, especially men who have had a negative biopsy in the past, and men who are considering or are on active surveillance. Again, we are not at the point of saying you must have an MRI before you're eligible for active surveillance. There are lots of reasons not to make a declaration like that; cost is just one.

Everybody who gives a lecture on MRI shows some case example of a patient who had a Gleason 3+3 on regular biopsy. Then an MRI shows a big anterior Gleason grade group 5 tumor. In that case, the MRI potentially saved the man's life. Those cases happen. The truth is that large tumor was probably visible on ultrasound too, but that issue aside, for every case like that, there are plenty of cases with the opposite outcome: What we thought was a 3+3 based on the standard biopsy turned out to include a tiny little speck of Gleason group 2 in the directed biopsy. Is this case eligible for active surveillance or not? Based on the standard assessment, he has low-risk disease. We've got reams of literature saying that low-risk disease based on transrectal ultrasonography (TRUS) biopsy does not need treatment. But now we've reclassified him, and now he is higher risk. Do we put that patient through treatment? There is a real overtreatment risk there. These are trade-offs. It's not an easy answer.

We do a lot of MRIs for men already on active surveillance. One of the big questions in surveillance is: can MRI replace the surveillance biopsy? If you've had a systematic biopsy including the regular, mapped-out biopsy, plus you have a baseline MRI that either shows a small lesion

"Prostate cancer is never an emergency. You can always collect more opinions."

that you've biopsied or nothing, then you could use the MRI to follow that man and do fewer biopsies. It is unlikely that you'll have a cancer not visible on high-grade MRI, a cancer that is missed on both MRI-guided and systematic biopsy, that will suddenly grow.

We're starting to selectively replace the active surveillance biopsy with MRI. MRI is not completely replacing biopsies by a long stretch, but it is replacing some biopsies for men at the lower end of the risk spectrum.

Because these men can go longer between biopsies?

Dr. Cooperberg: Yes. That's the idea. But none of this is standardized. The American Society of Clinical Oncology guidelines that came out last year on active surveillance are clear: surveillance is still based on PSAs and biopsies. Everything else—MRIs, etc.—is still experimental.

But MRIs are increasingly used in active surveillance, aren't they?

Dr. Cooperberg: They are, but lots of interventions get used without adequate data. Occasionally, we see patients who had an elevated PSA and were sent for an MRI that showed a lesion. The radiologist did an MRI-guided biopsy. The patient never had a TRUS biopsy. That is not appropriate in 2017. The MRI technology is not there yet. And I certainly don't think the expertise is

there yet. The imaging itself has a way to go. And there are other problems.

The Prostate Imaging Reporting and Data System (PI-RADS) is a means of standardizing the multiparametric MRI reading. The patient goes into the MRI magnet, which generates complex nuclear magnetic resonance (NMR) data, reams of molecular data at a very high level of resolution. The computer collapses that down into a grayscale picture for the radiologist to analyze. Based on the PI-RADS system, the radiologist assigns scores for each different sequence—anatomic, diffusion-weighted, and dynamic contrast—on a one-to-five or positive/negative basis. Then the sequences are combined to a one-to-five summary score—and generally, we dichotomize the scores: one to three is negative and three to five is positive. The information loss along the way between the magnet and the final clinical decision is a bit staggering.

Are there any other imaging techniques on the horizon that may replace the MRI?

Dr. Cooperberg: There is a lot of excitement for what will be the next-generation MR spectroscopy based on hyperpolarized Carbon-13 imaging. This is next-generation MR imaging in which we can essentially watch metabolic pathways unfold in real time at the millimeter level. That's going to be incredible. This technology was developed by John Kurhanewicz at UCSF and is in late-phase testing now. A few of these machines exist so far around the world; this may really be a game changer.

Technologies for next-generation ultrasound may also be able to yield a very high-resolution picture. These technologies have to be studied carefully head-to-head. It may bear out that better ultrasound technology will prove more cost-effective and easier on the patient than MRI, which requires separate visits, separate costs, and multiple physicians. Plus, MR is competing—especially when we talk about active surveillance—with blood, urine, and tissue biomarkers. Should a surveillance candidate who is on the edge get an MRI, a Decipher test, or both?

Would you use multiple tools or just one?

Dr. Cooperberg: Potentially multiple, but if everyone uses multiple tools, the cost increases exponentially. We don't always know what to do with conflicting information. If you have a reassuring MRI and a concerning Decipher score, what do you do? If you have a high biomarker score and the MRI still doesn't show anything, what do you do? These are challenging questions.

From a research standpoint, this is what makes it fun. But for the man on the ground, there is a lot of confusion. It's part of the reason that I'm skeptical about how aggressively a number of these tests are marketed in the prostate cancer community.

You mean how tests like Decipher are marketed in the community?

Dr. Cooperberg: And MRI. It's all in the same category. When I give a talk on MRI, I consider it to be a novel biomarker. It faces all the same challenges and has to play by all the same rules as Polaris or Decipher. You've got to prove that it's going to give you better information than you can get from the basic clinical assessment. You've got to prove it's going to help you make a better decision. And you've got to prove that it gets better outcomes, just like the biomarkers. Just as we're not quite there with the biomarkers, we're not quite there with MRI.

In other words, it is pointless if you live in a rural community to insist that your community urologist order all these tests without the urologist knowing what to do with the resulting information?

Dr. Cooperberg: I would say that's completely true.

What about PET/CT scans?

Dr. Cooperberg: The other emerging imaging story is PET/CT agents. We've historically done bone scans and a CT scan to rule out metastatic disease. That's been standard of care for a long time for men with high-risk prostate cancer. But the sensitivity is low. To light up one of those scans, you need 100 million cells in one spot. Now, we've got much more sensitive tests like PET/CT that can show much smaller metastases.

Sodium fluoride PET/CT is a much more sensitive way of looking at the bones. And just recently, a test called Axumin (fluciclovine F 18 or FACBC) has been FDA approved. It's a more sensitive way of looking at both bones and soft tissues for prostate cancer metastases. And PSMA-based PET/CT has the best sensitivity yet to find small metastases in either the bones or the soft tissues.

UCSF was the first center in North America to get PSMA PET imaging. It's been out in Australia and Germany for a number of years. We have scanned thousands of men. There is no question that it is more sensitive. But the question is: What do we do with the information?

There is a big body of evidence for those who have clinically localized, high-risk prostate cancer (e.g., Gleason grade group 5 in multiple cores). These are obviously bad tumors, but the bone scan and CT scans may be negative. In these cases,

the men will do better (live longer) if we treat the prostate aggressively with surgery and/or radiation than if they go on hormones alone.

Now with more sensitive scans, we show what we've known for many years: a lot of men in that situation had micrometastatic disease, but it just didn't light up on the scan. Now, with a super-sensitive test, we can identify the metastasis much earlier.

But what do we do with it now that we've found it? Do we call his cancer metastatic and say he's ineligible for surgery or radiation? Do we still offer surgery and radiation knowing that he will not be cured? How do we combine these treatments? Can we target radiation to spots that we see on these novel PET imaging tests? These are all big research questions that require bigger studies.

These more sensitive scans also teach us things we did not know about the spread patterns for prostate cancer. Canonical knowledge informs us that prostate cancer originates from the prostate and spreads out first to the pelvic lymph nodes, then other lymph nodes, the bones, the lungs, and to other places. We thought that the vast majority of the time it pretty much followed that order, but are now learning that is not necessarily true. In one of the first PSMA tests we did at UCSF, the pelvis was completely quiet, but there was activity up in the lymph nodes of the neck. My first reaction was that this was yet another false-positive imaging test. But the cancer had completely skipped the pelvis and gone straight to the neck.

Do we know why some prostate cancers spread in one way versus another?

Dr. Cooperberg: Genetics and biology. That is a very short answer for a whole different conversation. And frankly, it's still not that well understood.

What advice do you have for patients regarding imaging?

Dr. Cooperberg: Like with many questions in prostate cancer, you have to be a very educated consumer. Be very careful about separating science from hype. Many insurance companies are still reluctant to pay for MRI and many don't pay for the novel PET tracers yet.

What about participating in a clinical trial? Can patients get some of the imaging that way?

Dr. Cooperberg: That is always encouraged. First of all, it is a way to get some of these imaging tests done for much less money. I think you still have to have a conversation with your urologist about what to do with the information, though. Even if the test is done in a clinical trial, find out how it will change the way your doctor manages your treatment.

For example, we have a couple of imaging trials open at UCSF right now in which we're doing novel imaging tests before surgery. The protocol is explicit that if we have a negative bone scan and a negative CT scan, we make a plan for surgery. Then the patient gets a PSMA PET or a Carbon-13 MRI exam and if it shows us something we do not expect to see, we're still going to go forward with surgery. If there's a lymph node that lights up, we're going to try to take it out at the time of surgery. If there is something in the bones that lights up, we're still going to radiate it after the fact. We're not going to rule somebody out for surgery based on what we're still considering experimental or quasi-experimental imaging.

So then men should definitely ask their urologist how the imaging information might change things before the imaging study is even ordered?

Dr. Cooperberg: Absolutely. You should never order any test—imaging or otherwise—that is not going to change your management, not going to change what you do. Otherwise, there is no point in doing the test.

If your doctor doesn't have an answer to that question, should you find another urologist?

Dr. Cooperberg: I wouldn't get the test. I would get another opinion. Prostate cancer is never an emergency. You can always collect more opinions.

I think very few people realize that.

Dr. Cooperberg: I know. That's a point we have to make over and over again.

Cancer is frightening.

Dr. Cooperberg: I know, but everyone needs to realize that we use the "C" word for a lot of things that can happen in life. Pancreatic cancer is on one end of the spectrum and prostate cancer is at the other end. It's very uncommon that prostate cancer needs to be treated within days, weeks, or even months.

You have the leisure of educating yourself.

Dr. Cooperberg: There is always time to collect a couple of opinions. These are permanent, potentially life-changing decisions. It's much worse to end up regretting your choices for decades than to spend some extra time getting educated. Pp[1]

Michael Zelefsky, MD

Imaging + Radiation Therapy

Dr. Michael Zelefsky, a radiation oncologist, is Professor of Radiation Oncology, Chief of the Brachytherapy Service, and Co-Leader of the Genitourinary Disease Management Team at Memorial Sloan Kettering Cancer Center in New York City.

Prostatepedia recently spoke with him about how advances in imaging have impacted radiation therapy.

What attracted you to medicine?

Dr. Zelefsky: What has attracted me to medicine is the opportunity to provide direct help and assistance to people, especially in oncology. There are many excellent treatment options in particular for organ-confined prostate cancer. Unfortunately, patients often find themselves confused about the optimal direction or type of treatment intervention that would be best suited for their disease. Given the massive amounts of information out there on the Internet as to what should or could be done, there is often a great deal of confusion. The ability to provide that clarity, provide direct assistance, treat people, and make a difference in their lives has always been very important to me.

In addition, my father is a practicing diagnostic radiologist, and he has always served as a role model for me.

"My father is a practicing diagnostic radiologist."

I went into radiation oncology with the keen interest in not only utilizing sophisticated imaging technologies to further advances in medicine but also to directly interact with the patient as well. I see my career as having been a fusion of imaging, direct patient care, and clinical research.

What role does imaging now play in radiation therapy?

Dr. Zelefsky: Radiation therapy has been linked to imaging for many years. In the late 1970s and early 1980s with the advent of the CAT scan, those images were used in the treatment planning process to provide greater accuracy for targeting the radiation. Over the ensuing 20-30 years, there have been significant advances in imaging, from CAT scanning to MRI, and from multiparametric MRI to molecular imaging. These advances in diagnostic imaging continue to be linked to radiation treatment.

We use multiparametric MRI imaging to target radiation to the prostate with exquisite precision. Just as importantly, we use these technologies to understand the geometry and anatomy of the surrounding normal tissues. For the prostate, that could mean the bladder, rectum, bowels, and even specific anatomic regions like the bladder neck and the neurovascular bundles, that control erectile function.

Advances in imaging have allowed us to visualize these normal tissue structures, and this information is incorporated into treatment planning, giving us a way to deliver the radiation with a precision we've never had before.

What sorts of changes do you think are on the horizon as we develop better imaging techniques?

Dr. Zelefsky: We have successfully moved from CT-based imaging to MR-based imaging. Now, we commonly use MRI and fuse those images with the CAT scan. At Memorial Sloan Kettering, we have moved to the next step, which is pure MRI-based planning. This means we don't need the intermediary step of a CT scan anymore. We can plan directly off the MRI, and we map everything out from these sets of specific

images. The image fusion step is, therefore, no longer necessary.

We've also moved beyond MRI to what we call multiparametric MRI. We look at different sequences and formats of the MRI, including dynamic contrast enhanced imaging, and diffusion-weighted imaging to give us further information about the location of the disease within the prostate, which is called the dominant intraprostatic lesion (DIL). This dominant intraprostatic lesion is an important area to target because recurrences after radiation stem from regrowth of disease from that initial site of disease in the prostate.

Radiation oncologists are recognizing that there may be opportunities to intensify the focus of the radiation to the DIL to improve the tumor control rates with radiation. We have moved from CT-based to MR-based radiation therapy to pure MRI-based planning, and now we incorporate important information from multiparametric imaging. In the future, we'll also incorporate molecular imaging, which comes from advanced nuclear medicine studies.

In the US, is there a big discrepancy between centers of excellence like your own that can perform and read MRI and smaller community centers where perhaps they're not as capable of reading and interpreting the results? Does that discrepancy in skillset translate into a difference in radiation planning?

Dr. Zelefsky: Well, of course. While they haven't yet proven to be associated with superior cure rates, we recognize that integrating these new imaging modalities into radiation enhances our precision, and greater precision in radiation therapy planning generally means reduced exposure to normal tissue structures. In turn, this means reduced side effects. Enhanced imaging precision allows radiation to be delivered with less toxicity than before. In time, many centers will incorporate MR scanning with their radiation. Already, commercial software is available that allows image fusion of MRIs and CT treatment planning as well.

With these advances in MR and molecular imaging, the radiation oncologist must work with a multidisciplinary team of diagnostic radiologists, urologists, medical physicists, and other parts of an oncology team as treatments will be enhanced in this way. We need skilled and experienced diagnostic radiologists in the area of prostate radiology to work closely with the team to come up with optimized plans. Radiation oncologists don't work in a vacuum.

Do you think molecular imaging will be incorporated soon?

Dr. Zelefsky: There's a lot of excitement with PET/CT imaging. PET imaging fused with MRI is also emerging now. This has been used effectively for various disease sites, not only prostate cancer. For prostate cancers specifically, newer PET tracers such as PET C-11 Choline and exciting developments in PSMA tracers will be used. These provide us unique opportunities to see where micrometastatic disease could be lodged. That information is critical for the radiation oncologist to pinpoint the disease.

There are also exciting developments using some of these tracers as a form of therapy. Tracers such as PSMA are linked to lutetium-177 and tracers can be integrated with radiation planning as well. We are on the verge of seeing these new developments; these changes will soon be integrated with radiation.

Is there anything else you think patients should know about imaging's role in radiation therapy?

Dr. Zelefsky: With new advances in imaging and by working in close collaboration with diagnostic radiology, we are getting much more accurate information concerning where microscopic disease is located and the critical zones within the prostate where tumors are lodged. We use imaging to consider re-biopsying patients where there may be a discrepancy between what looks like earlier states of disease, but the MRI shows there is greater volume of disease than what was anticipated. We need to know this information in order to plan the radiation well. We need to consider opportunities to intensify the dose to the DIL in the prostate and whether there is nodal disease and where exactly the nodal disease could be within the pelvis.

Imaging plays a huge role in our follow-up with patients, allowing us to detect recurrences earlier than ever before. This is vital information for patients because earlier detection of recurrences allow for salvage therapies much sooner and treating such patients at earlier time points is often associated with more successful outcomes.

In the future, imaging will help us consider focal ablative therapies where the paradigm is shifting in earlier cancers. Simply put, we could just focus on the DIL and spare the rest of the prostate if we can be sure that there is no significant disease in other parts of the gland. There have been a number of efforts to use focal therapy with advanced imaging to small subunits of the prostate. So new imaging possibilities are opening up new directions and opportunities in the treatment of prostate cancer. Pp[1]

Raoul Concepcion, MD
Imaging + Urology

Dr. Raoul Concepcion is the Director of The Comprehensive Prostate Center in Nashville, Tennessee, and a former President of the Large Urology Group Practice Association (LUGPA).

Prostatepedia spoke with him recently about the impact advances in imaging have had on urology's approach to prostate cancer.

Why did you become a doctor?

Dr. Concepcion: My father emigrated from the Philippines in 1955 to start his general surgery residency.

My mother came over in 1957 with my brother and sister; I was the only one in the family born in the United States. I was born in Ohio where my father was a general surgery resident in the Youngstown area.

When he finished his general surgery training, he and my mother were going through the naturalization process to become US citizens. He was therefore unable to set up a practice at that time. Through a mentor and friend, he was invited to become one of the first residents in the newly established urology program at the Lahey Clinic in Boston. We moved to Boston for a few years, and when he finished his urology residency, we moved to Central Ohio where he was one of the original seven physicians in what is now a 75+ multispecialty clinic in Marion, Ohio.

"By the time I became old enough to work, I would scrub with my dad in the operating room."

By the time I became old enough to work, I would scrub with my dad in the operating room, along with working many other jobs in the hospital, including positions in radiology, physical therapy, and as an orderly transporting patients.

I have been around medicine my whole life. We never sat down for long, in-depth conversations about what I would study in college, but my father's only piece of advice was that the great thing about medicine is that you essentially work for yourself. It's not so much true these days, but back then you could set your own schedule and essentially work independently. He said if you take good care of patients and they get better, you can take a fair amount of credit for that. But, he said, if patients don't do well, we have to take responsibility for that, too. That sent me on my way.

Did your siblings go into medicine as well?

Dr. Concepcion: Yes. My brother is a urologist. He and my father were partners together in Ohio for a few years. My sister is in the business world.

How have some of the newer imaging techniques changed the way we determine which patients should have prostate cancer surgery and which should not?

Dr. Concepcion: If you look back to the early 1980s, there was no reliable method to determine whether you should have a biopsy or not. Urologists did biopsies if we felt an abnormality on a rectal exam. Without imaging to do the biopsy, it was completely blind. We could either do it transrectally with a big needle—which resulted in a significant incidence of sepsis, bleeding, hospitalization, and infection—or, more commonly, a triangulation method. With one finger in the rectum, you would anesthetize the perineum. Then you would put a needle through the perineum and guide it with your fingers into the prostate without taking off the top layer of your finger. It was a rudimentary and archaic method.

The first breakthroughs in diagnosis came with the development of transrectal ultrasound and PSA (prostate-specific antigen) in the late 1980s. The ultrasound equipment was relatively inexpensive, allowing urology practices to purchase it easily. PSA was a blood test that had been recently approved during the same time period. However, as the name implies, it is prostate specific, but not prostate cancer specific.

The incidence of prostate cancer in the pre-PSA era was somewhere around 50,000 new cases every year with over 50% of those cases being extracapsular, making cure unlikely. In just a few years after the introduction of transrectal ultrasound and PSA, there was a marked jump in the number of men diagnosed—to over 200,000 cases with less than 10% of those being extracapsular. People assumed this jump was because of PSA, but they forget about the development of prostate ultrasound.

For the last 30 years, we have been woefully under-staging and underdiagnosing prostate cancer as prostate ultrasound-guided biopsy is sampling less than 1% of the prostate. The standard across the United States is a sextant biopsy with 12 biopsy cores taken, two per sextant. It is a systematic approach, but it's random as ultrasound is not a diagnostic test, telling us normal or abnormal. We're just arbitrarily dividing up the prostate into the six areas and randomly placing our biopsy needles for the majority of the cases. So, if you have a negative biopsy, is it truly negative? If you have a positive biopsy, do you know that what you're sampling represents the true tumor biology of the prostate? In any given patient, biopsy may detect what looks like Gleason 3+3 in one area, but there may, in fact, be other areas that have clones of different/higher grades that were not detected on biopsy. This is the heterogeneity of prostate cancer. Prostate ultrasound and biopsy are the weakest steps in diagnosis.

"MRI is not perfect."

What are some of the newer diagnostic breakthroughs?

Dr. Concepcion: The first major breakthrough that has been championed in Europe and is gaining significant traction now in the US is multiparametric MRI of the prostate. Due to advances in technology, we're able to identify lesions of interest that could harbor higher-grade Gleason. It becomes a true diagnostic test just like a CT scan or an MRI of a kidney. If a patient truly has a majority Gleason 3+3, he is a candidate for active surveillance. But MRI is not perfect. The challenge is not to detect prostate cancer, but rather significant prostate cancer that does require treatment, which for the most part are higher-grade Gleason grades of 4 and 5.

Does multiparametric MRI allow you to better target which parts of the prostate to sample?

Dr. Concepcion: Multiparametric MRIs are hard to read, so you've got to have a good radiologist. In this world of value-based medicine where we try to contain costs, this means bringing in another specialty. Urologists depend upon the radiologists. So, assuming the radiologist can detect the lesions, the questions are: How do you then direct your needles? What other equipment/technology is required? Can you do it under MRI guidance? That is where the term fusion biopsy comes into play.

There are two types of fusion techniques for the most part: cognitive and mechanical. The biopsy, in either case, is still ultrasound-guided by the urologist. Cognitive refers to knowing where the lesion of interest is located based on the MRI and concentrating where to direct the biopsy needle based on that knowledge. Mechanical requires special software to match, or register, the ultrasound and MRI images. The MRI image is loaded into this registration unit and the ultrasound image that the urologist is performing in real time fused, or superimposed, over the MRI image. So, even though we're using ultrasound, it looks like we're biopsying off the MRI.

Is that now a widely accepted practice in community settings?

Dr. Concepcion: Not every community is blessed with a really good radiologist.

Another problem is that the registration unit that is required to fuse the images together costs somewhere between $150,000 and $300,000. It's better medicine and better technology, but because the reimbursement rate is only slightly higher, it could be a financial loss. A number of groups and institutions have gone ahead and purchased this equipment, but there is a significant learning curve.

In Europe, Dr. Mark Emberton and his colleagues are recommending that urologists use MRI as a screening test to determine whether or not you should get a biopsy. We are not there yet in the US.

They have a different healthcare system in the UK, with a different set of priorities.

Dr. Concepcion: It's completely different. But that's how things are

"Not every community is blessed with a really good radiologist."

evolving. The standard ultrasound is 9.5 megahertz. If you go to a higher megahertz probe, you can technically get better resolution.

A couple of companies here in the United States are marketing high-resolution ultrasound. The beauty about this is that it may be a little bit more expensive than traditional ultrasound, but you don't need MRI or radiologists. You continue with a workflow that is very much in line with what you do now because it's just high-resolution ultrasound.

In terms of surgery, MRI could be useful in defining extent of disease/extracapsular disease for those patients diagnosed with higher-grade cancers that are contemplating treatment.

Would that mean fewer patients will need a biopsy?

Dr. Concepcion: Right. Only men who had a positive MRI would get a biopsy. Again, if we believe that patients who truly harbor only Gleason 3+3 do not need treatment, then the challenge is to biopsy only those that have a higher possibility of having Gleason 4 or 5. In terms of the patient who is requiring treatment, we would want to see whether or not he has capsular involvement and whether it involves one bundle. The radiation oncologist would look at this in terms of surgical planning for the tumor itself because MRI could give you a better anatomic view of the prostate at the time of surgery.

What kinds of imaging are you using now in surgery planning?

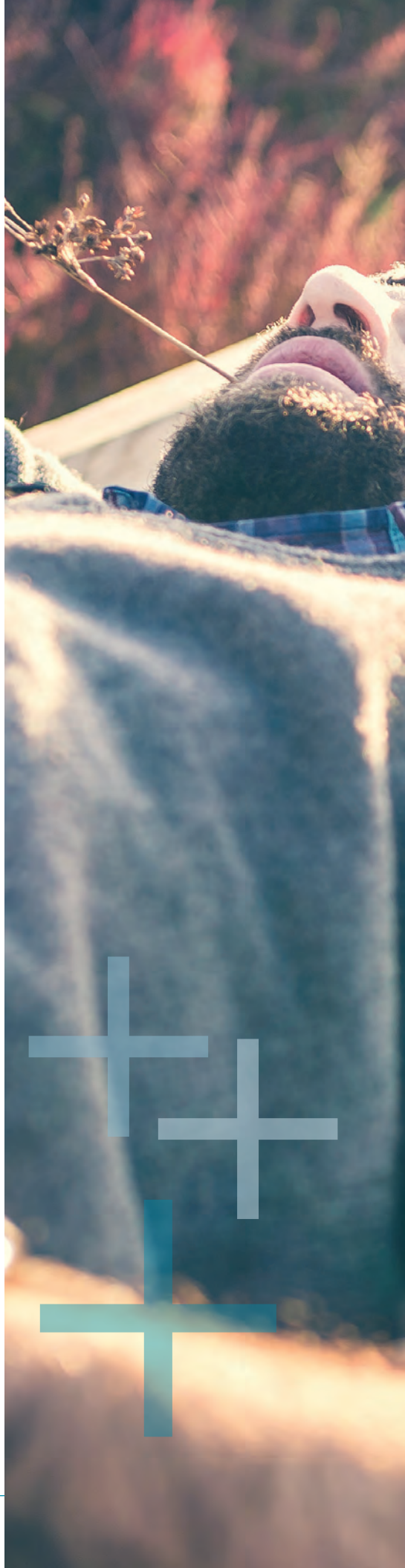
Dr. Concepcion: We don't really need a lot of imaging to determine how we'll manage the primary care of most tumors, even if they're higher grade. It's not really that helpful. As mentioned above, it might play a limited role in preoperative staging and planning.

Advanced imaging may play a bigger role when we stage workups for high-grade disease to determine whether or not a patient has metastatic disease. This plays a role in how to treat the primary tumor in the setting of oligometastatic disease. The traditional staging workup for a patient with high-grade cancer is bone scan and CT, which have lower sensitivity than some of the newer modalities like sodium fluoride PET/CT, C-11 Choline, PSMA, or Axumin. All of those newer scans are being used for the detection of metastatic disease and rising PSA after therapy.

If they start to gain approval for use earlier, in initial staging at the time of diagnosis, we might find areas a bone scan or CT would not, especially in patients with high-grade cancers. One of these new advanced imaging scans might show areas suspicious for metastasis.

The question then becomes: What do you do with that patient?

I trained in the 1980s when Dr. Patrick Walsh first pioneered nerve-sparing radical prostatectomy and defined the anatomy of the dorsal vein complex so that we markedly reduced blood loss at the time of surgery. A pelvic lymph node dissection is part of the procedure. During that time, however, we would not remove the prostate if the lymph nodes were positive on frozen section, thinking that the tumor had already spread, making cure unlikely.



"Advanced imaging may play a bigger role when we stage workups for high-grade disease to determine whether or not a patient has metastatic disease."

In the few cases that we did just that with high-grade disease, most of us regretted the day we left the tumor in place. The majority of those patients were started on hormonal therapy, failed, and ultimately developed significant local disease, including bleeding, urinary retention, pelvic pain, and ureteral obstruction.

There is a growing consensus that we ought to be very aggressive with the primary tumor in that situation—take it out or at least treat it. We know that when tumors spread out from the prostate, they go into the lymph nodes and then bone in an orderly spread. (This is the concept of seeding and branching.) Recent studies show that those metastatic sites will clone, so you may have a clone that goes to the rib, the lymph nodes, and/or the periaortic area. Those clones can then go back and reseed the prostate. The way the cancer spreads is not a one-way street. Spreading is bidirectional. Your tumor acts like a potential reservoir unless you take it out.

Would you remove the primary tumor and these different oligometastatic sites through surgery or medication?

Dr. Concepcion: You would treat the primary with surgery and/or radiation, but then you would aggressively start the patient on androgen deprivation therapy, chemotherapy, immune therapy, or radiation. You wouldn't necessarily take out those metastatic sites. You wouldn't take out a rib, for example, but you would immediately start therapy. It's not just going to be surgery or just radiation. We're going to throw the book at it.

What if the metastatic sites are in pelvic lymph nodes—somewhere where it would be easy to remove?

Dr. Concepcion: You would know that up front and you might do an extended lymph node dissection.

Some of these newer scans have been done in patients whose PSAs start to go up after radical prostatectomy. We identify soft tissue lesions that had maybe been missed or grown. Surgeons then go in and remove them. If through this advanced imaging, we see an area that's surgically accessible, then absolutely we could go back in and take out the tumor or the metastasis.

Are these newer imaging techniques available in most communities?

Dr. Concepcion: Axumin and C-11 Choline are approved by the FDA. But no, they are not uniformly available to the common urologist right now.

Do you think it would be in a man's best interest to travel to get these scans?

Dr. Concepcion: It depends upon the grade of his cancer and where he is in his treatment. It depends upon what part of the disease spectrum he currently lives. Pp1

William Goeren, LCSW-R: Gay Men + Prostate Cancer

William Goeren is the Director of Clinical Programs for CancerCare, a New York-based organization that offers counseling, support groups, education, and financial assistance to cancer patients and caregivers.

Prostatepedia spoke with him about common issues gay men with prostate cancer face.

Why did you become a social worker?

Mr. William Goeren: I became a social worker in the mid-1980s in response to the AIDS crisis. This was not the direction I was headed, but the AIDS crisis had so shifted my outlook on life and altered my priorities that I needed to figure out a new direction, a new version of myself.

Like many young men in their early twenties, I had come to New York with dreams of a fulfilling acting career. In the midst of that, I had a shift in priorities. It was a rather dramatic shift. I was just trying to come to grips with grief, loss, death, and dying. And that's when I attended a five-day workshop called "Life, Death, and Transition" presented by Elisabeth Kübler-Ross in upstate New York. Every day we had workshops, presentations, and individual work in her intervention model designed to help people understand death. It was very powerful to be in her presence. I knew who she was prior to going and was rather in awe of her.

After that workshop and others with a number of other high-profile people of that era, a hospice nurse strongly stated I would make a wonderful social worker. I applied to school, and my path very much changed at that point. I felt very passionate about my new direction.

How did you start at CancerCare and what do you do there?

Mr. Goeren: Earlier in my career, a gay male client in his early 30s who had a rare salivary gland cancer came in to where I was working and said that he was scarred after surgery and radiation. He said: "As a gay man with cancer, there are no services for me at all. If I had HIV, I would have services from A to Z."

That comment stuck with me, so when I got to CancerCare in 2008, I started working on an LGBT cancer program here. In 2011, I collaborated with a New York organization called Services & Advocacy for GLBT Elders (SAGE), which provides psychosocial and concrete services for gay and lesbian elders. We launched a face-to-face support group for older gay men with cancer. That was the first actual service that we were able to launch. Though there's a wide range of cancers in the group, the majority of the men have prostate cancer.

We've made attempts to launch other services; some are more successful than others. We started a group for gay women with cancer here in New York, but it was difficult to populate and maintain. We launched

"We launched a face-to-face support group for older gay men with cancer."

some online support group services, which are very robust and are for our national LGBT clients. There are currently two online groups for the LGBT community, one for LGBT cancer caregivers and the other for LGBT persons with cancer. Eventually, I would like to launch an online support group for the LGBT community who are bereaved because of cancer. We have a few publications, and I've done some talks at some of the national oncology social work conferences. In general, CancerCare

now has 42 online support groups, which are social worker-facilitated, password-protected posting boards. These are not live groups but very much function like a face-to-face group.

What are the particular concerns or challenges facing gay men with prostate cancer?

Mr. Goeren: There is some research going on that is limited and minimal. For example, David Latini, Daniela Wittmann, and Thomas Blank are doing research focusing on issues in the LGBT community and cancer and, in certain studies, research specifically related to gay men who have prostate cancer. They are interested in how gay men, differing from their heterosexual counterparts, react to being diagnosed; the impact of the diagnosis and treatment on their sense of self, emotional well-being, and quality of life; as well as how the medical community could be more sensitive and better trained in LGBT and cancer issues.

Research has shown that many gay men feel great shame, stigma, and embarrassment triggered by their emotional reactions and the physical changes related to prostate cancer and its treatment. This shame and stigma touches upon, for many, established internalized homophobia, previous experiences of discrimination and harassment, history of coping with, and in some cases, living with HIV disease, and negative experiences coming out.

Many men experience urinary and bowel incontinence, altered sexual function, and penile shortening (an underreported and under-discussed side effect). All of these impact a sense of masculine identity for men in general. For many gay men, prostate cancer can have a compelling and compromising impact on one's sense of self within an already disenfranchised and diverse community, his self-esteem, and his ability to relate intimately to other gay men. Gay men report losses associated with prostate cancer for both the man with cancer and his partner. These losses include spontaneity, intimacy, and normalcy in sexually relating, which can lead to fears of rejection, emotional withdrawal, depression, and anxiety.

In addition, HIV affects many gay men who have cancer, whether they live with HIV, have survived multiple HIV-related losses, or are coping with issues of safer sex and determining their risk of exposure and infection.

Another immense challenge for a gay man with prostate cancer is finding an oncologist who is educated in the complexly sensitive and layered issues that confront any gay man with prostate cancer. It is essential that an oncologist provide a comfortable, secure, and safe atmosphere in which a gay man can disclose and discuss his sexual orientation, lifestyle, and activities.

If you can't be honest with your doctor or if you feel like you're going to be judged…

Mr. Goeren: Yes, and it works on a number of levels. Research has shown that a significant portion of LGBT communities, including gay men, are wary of disclosing because they fear compromised service from all levels of the medical community (nurses, social workers, and receptionists), covert or overt discrimination, and poor-quality care. An LGBT person walks into a hospital, cancer, or medical center and wonders if they are going to feel welcome and safe. That starts with the security guard, through the receptionist, to the nurses, the doctor, and beyond.

"Many gay men feel great shame, stigma, and embarrassment."

In the support group I run in collaboration with CancerCare and SAGE for gay men 50 and older, only half stated that they were out as gay to their oncologist. This parallels their lives as well: men who are fully out in life tend to be fully out to their oncologists. When I asked the gay men who were not out why they had not disclosed to their oncologist, they said, "The doctor didn't ask," or "It wasn't asked in the intake forms," or "I didn't think it was important." The medical community is primarily a heteronormative model.

These kinds of subtle messages and experiences compile so that someone may not feel safe or comfortable disclosing their sexual orientation within the medical setting. Then there are the more overt experiences of discrimination, harassment, and even hostility when an LGBT person discloses their orientation identity. The Minority Stress Model conceptualized by Ilan Meyer states that LGBT minorities have potential for poorer psychological well-being when chronically experiencing even subtle forms of discrimination, oppression, and healthcare inequities and disparities.

Does the discomfort with identity disclosure extend to other areas of care, such as reluctance to discuss potential side effects? If a patient feels uncomfortable in one way, is he uncomfortable in all ways?

Mr. Goeren: Yes. And this affects conversations about prostate cancer and treatment. It also has ramifications for general health. People are fearful of bad treatment, and in very rural communities, report fear for their physical safety.

If you can't come out to your doctor, your doctor is not going to be able to order the appropriate tests, scans, and bloodwork, or discuss healthcare concerns and risks, which will, ultimately, affect your quality of health. And in terms of prostate cancer, a doctor without knowledge or understanding of the world of a gay man, who does not understand how prostate cancer will impact the life of a gay man, will not be able to provide the appropriate and essential medical and emotional care. Necessary discussions about how treatment may affect their lives, quality of life, and genitourinary and sexual performance will not happen. A gay man might refuse to discuss with that doctor how treatment will affect him.

Because that conversation is so important, is it more difficult for gay men after surgery?

Mr. Goeren: It's a general concern for those with prostate cancer. Regardless of sexual orientation, most men feel that the side effects of treatment are whitewashed, minimized, or not fully explained and that they're not given a thorough description of the potentials and possibilities. Whatever the combination of treatments, when men experience severe urinary incontinence, bowel incontinence, or any kind of sexual dysfunction, most men that I've talked to have said that had the consequences been more fully explained, they might have made other treatment choices.

Gay men have different sexual lives than straight men, so the issues of sexual function are very different. When impact on sexual function is ignored, glossed over, or minimized, it's even more difficult for a gay man to have that conversation with the doctor, especially if the doctor does not overtly state their comfort level or background in training and working with the LGBT population.

What services does CancerCare offer gay men with prostate cancer?

Mr. Goeren: CancerCare does not have specific services for gay men with prostate cancer. There might be an expressed need, but to launch a support group whether in-person, on the phone, or online, if you don't have enough clients in the group, it ultimately is not feasible to start or continue a group. We created a face-to-face group for older gay men with any cancer, an online group for all LGBT persons with cancer, and an online group for LGBT cancer caregivers. CancerCare's online group program serves our New York tri-state and national clients.

I would like to provide online bereavement services for national LGBT populations affected by cancer in the spring of 2018. But I don't know if there is enough of a population or referrals to launch something.

What kind of services does CancerCare provide for individual men in need of support?

Mr. Goeren: We provide them information and speak with them,

"It is essential that an oncologist provide a comfortable, secure, and safe atmosphere."

but mostly we make referrals to the limited resources like Imerman Angels, which does peer matching. For men in suburban or rural areas who may not have access to community resources, we make referrals to such organizations as the National LGBT Cancer Network or the Gay and Lesbian Medical Association and help them find support and even medical resources.

What should a gay man who lives in a rural or suburban area do if he doesn't feel comfortable talking to his doctor about these issues?

Mr. Goeren: There are a number of national resources. The Gay and Lesbian Medical Association (http://www.glma.org) is a predominant resource. They could also contact the National LGBT Cancer Network (http://cancer-network.org), which maintains a list of either LGBT-sensitive oncologists or oncologists who are themselves LGBT. There are also prostate cancer organizations like Us TOO International (http://www.ustoo.org), which provide peer support and have an extensive resource list. And of course, CancerCare.

CancerCare has three modalities of counseling care—face-to-face, telephone, and online group counseling. We have individual and group face-to-face support counseling for clients in the New York tri-state area. And one of our primary counseling services is individual phone counseling, which is for our national clients. We also have a number of telephone group clients from all over the country. Finally, we have a very robust online support group program, which includes the LGBT Cancer Caregivers online support group and the LGBT Persons with Cancer online support group.

Do you ever pair patients with peers for personal one-on-one support?

Mr. Goeren: We do that informally. The primary mission of Imerman Angels is to provide one-on-one connections with their peer matching modality, and it's wonderful and important. It's essential to talk with a professional, but sometimes there's nothing like talking to somebody else who's going through what you're going through.

Do you have any advice for gay men with prostate cancer?

Mr. Goeren: Make sure that you feel comfortable discussing who you are and who you love with your doctor. Find an oncologist with whom you can be yourself, where you can have the important and necessary discussions about who you are and who you love, and where you feel comfortable bringing your partner to appointments. Call one of the organizations listed above. Call Imerman Angels and find a peer. Get advice, strategies, and directions from other gay men who have been through this. Talk about the impact on your quality of life, your fears of recurrence, the impact of treatment on your sexual functioning, and your identity as a gay man.

Do you have any thoughts for heterosexual men who want to provide support to their gay peers?

Mr. Goeren: Heterosexual men can try to understand that, although there are similarities in how gay men respond to prostate cancer and treatment, this might be a different journey for gay men. There are many things they can share and discuss. But many gay men are not partnered, not in long-term relationships, and don't have the familial support that a lot of heterosexual men have. As we discussed, many older gay men and gay men in suburban or rural areas may not feel comfortable or able to disclose who they are and don't have the familial and community support that many heterosexual men or gay men in urban areas might have. These are obstacles to quality of care.

In terms of the impact of prostate cancer treatment on sexual functioning and intercourse, the strategies and techniques that may be useful for straight men will probably not work for gay men because we're talking about different sexual activities. In terms of the side effects, such as urinary and bowel incontinence, these also can be very different issues for gay men. Will I be able to participate in sexual intercourse? What does it mean if I can't engage in receptive sexual intercourse with my partner? How does that impact my relationship? How does this impact my identity as a gay man?

On a more global perspective, hospitals must make concerted efforts to be more inclusive and less heteronormative in practice and documentation (e.g., paperwork, assessments, and intake forms). They should also post nondiscrimination policies in public areas and spaces. These are elements that LGBT people scan for when looking for safe, inclusive health centers. For example, New York City's Health and Hospital Corporation hired the National LGBT Cancer Network to do LGBT cultural competency and sensitivity training about the LGBT populations for staff at all public hospitals. Anyone working in a public hospital in New York City has to have these trainings. These are incredible initiatives and long needed everywhere. Pp1

Patients Speak: Spencer Le Gate Facing Mortality

Mr. Spencer Le Gate spoke to *Prostatepedia* about his prostate cancer journey and his role in his local support group.

How did you find out that you had prostate cancer?

Mr. Spencer Le Gate: My family doctor put me on a small dose of a statin drug for cholesterol back in 2000. He had the good sense to give me a blood test every three or four months to check all my vital organs for any problems. At the end of 2007, he noticed that my PSA had started to rise. He asked if I knew anything about prostate cancer. Just a month prior, a childhood best friend had died from prostate cancer, so that was my introduction.

We watched my PSA for about a year, and then, in early 2009, I had a biopsy. We determined that mine was not the most aggressive form, so given all of the options, brachytherapy seemed like a good choice. I had the procedure in May of 2009. After that, there was a small spike in my PSA, which we all hoped would diminish as often happens after treatment.

"I took a 12-week course of training sponsored by a local cancer organization."

Almost two years later, my PSA had gone from around 1 up to almost 11, and that meant I had a recurrence of prostate cancer. Around early 2013, I had a biopsy that confirmed that I was recurrent nonmetastatic. I went on Lupron (leuprolide), which brought my PSA count down very nicely, so I asked if I could do it intermittently.

You asked for that rather than the doctor suggesting it to you?

Mr. Le Gate: Yes. I wanted the vacation because, of course, I experienced side effects.

What kinds of side effects did you experience on Lupron (leuprolide)? How did you manage them?

Mr. Le Gate: The side effects for me were, of course, the most common: hot flashes. At one point, I did have a Depo-Provera (medroxyprogesterone)

shot, which diminished the hot flashes pretty well. The others were loss of libido and muscle weakness. I have lost muscle mass throughout my body, but particularly, in my legs. My muscles atrophied.

Were any of these side effects severe?

Mr. Le Gate: I would say, for the first round of my treatment, not so much. But since I went back on Lupron (leuprolide) in 2013, they are more pronounced. When I took the vacation, my PSA went up alarmingly. In other words, it was worse than that scary doubling threshold in three months.

Did they put you back on the Lupron (leuprolide) as soon as that started to happen?

Mr. Le Gate: I've been on the Lupron (leuprolide) for almost two years. Now, when I get up in the morning, my legs are painful and I'm a little rickety.

Despite the fact that I'll be 75 in a few months, my legs have been good to me, and I've led a very active lifestyle. The pain I feel now in the legs is not just the inevitably of age, but the Lupron (leuprolide).

Does exercise help with the side effects?

Mr. Le Gate: Exercise does. I have backslid some, but until about a year ago, I had a trainer. I went several times a week. I took a 12-week course of training sponsored by a local cancer organization during the intermittent period and it was very beneficial. Should I get the motivation to get back to exercise, it would help me a lot. I am still active and hands-on in my profession. I'm a general contractor. It's a pretty active job, and I'm up and down all the time. But I learned very quickly once I started aerobic exercise, that it's more effective than getting up every morning and putting on my tool belt.

Is there anything else that you do to manage the side effects?

Mr. Le Gate: Of course, the change in your mental state. When I'm not working, I'm a person who spends a lot of time reading, and before I decided to become a contractor, I had a pretty good education. I have some sense of my cognition, and I think that your overall mental state has an effect on how well you feel.

Did that go away when you went on the intermittent period?

Mr. Le Gate: It did. Most everything went away. I only had a year. During the intermittent period, I took that phenomenal 12-week course. We met twice a week for two hours of rigorous training, weightlifting—everything. It was really eye opening for me.

Are you saying the exercise and training impacted the cognitive side effects you were feeling as well?

Mr. Le Gate: Oh, yeah. I think it did. I had some sense of that even before I had cancer. If you're physically active, there is a positive mental effect to that. Again, some of these things are just so blurred. How much of it is due to aging, and how much is just the burden of a disease that—at this point—cannot be cured?

Stress, you mean?

Mr. Le Gate: Yes, stress. Also, I always have been a bit anxious. Now I think I have to be more careful about managing my anxieties. I mean, I think there's so much of this disease that can be managed. You can manage it. I don't have a metastasis. So I'm not in a worse position.

I attend a monthly prostate cancer support group here in Sacramento, California. It's one of the best things I've done. I've gotten involved in it, and I've actually had the good fortune to be asked to lead groups, come up with ideas, and answer folk's questions.

I've had a very healthy life and getting a major disease like this has been instructive. I started reading and writing more because of it, even just letters to the paper, letters to friends.

About your disease?

Mr. Le Gate: Not necessarily, no. I'm a political person on the progressive side. I have very strong opinions that I don't mind sharing. Of course, I'm obliged to do more reading and be more thoughtful about my politics. I think having prostate cancer at this stage of my life has pushed me into this, and I take a great deal of satisfaction out of doing it now.

What advice would you have for a man diagnosed with this disease?

Mr. Le Gate: Find out all you can. Get involved in a group. Neither my oncologist nor urologist ever mentioned support groups. I discovered this just by chance when I was well into the recurrent part of my disease. Had I known that there was such a group when I was first diagnosed, I would've been better prepared to make decisions. Your doctor is a human being who can make good and bad choices. You need to be proactive.

I was fairly proactive, but when I first was diagnosed with the disease, had I known there was a support group, I would've learned about a number of other options.

For example, there's a group in San Francisco called The Second Opinion. Once you get a diagnosis—for no charge at all—you can meet

with a group of doctors and discuss your options. I never knew there was such a thing before. Everybody who's ever discussed the options thoroughly and looked at all sides of the coin can set their mind at ease before they make any decisions.

Are there other ways that the prostate cancer diagnosis might have had a positive impact on you?

Mr. Le Gate: After a lifetime without serious health problems, it's not a bad thing to realize that you're mortal. I think it's made me more responsible about whatever time is left of me. I want to use my time the best way I can and to learn something, even if it's just to learn something about the disease.

There's so much to learn about healthcare and the science of treating with medicine, but most people, if they're healthy, simply ignore this. To be more informed in this way, and to have the disease yourself—if you're smart and if you have a sense of humanity—you're going to think about other people who have the disease and be more sympathetic to others.

The diagnosis has made you more—

Mr. Le Gate: Empathetic.

I want to reach out to the people I see at my support groups because I know something about the disease, especially for those who have just recently been diagnosed. Because I know a bit more, because I'm old hat, if I'm able to do the slightest thing to relieve their anxieties and fears, that's a good thing.

I'm hopeful that I can put together some sessions at my prostate cancer support group where participants can discuss their mental state. At the last meeting, when I was asked to be the facilitator, I came up with the idea to put together a questionnaire, which would be voluntary and anonymous. I want to see what people have done to mitigate, find some distractions, and to discuss anxieties.

I've noticed in our group that we've discussed the mechanics more than the emotional. You have to be careful that you don't make this into a weepy, touchy-feely thing. I'm trying to navigate it so that we can discuss our emotional things in a sensible way that's helpful, that doesn't make people more fearful.

You want it to be a positive experience?

Mr. Le Gate: Exactly. I was pleasantly surprised when I raised the point, which was so different than the things we usually talk about. We usually talk about where someone is in their treatment. The response was relatively positive from people.

It's an Us TOO through the University of California Davis Medical Center and Dignity Health. We alternate between those two venues.

I've been with this group about three years. I'm not a person who joins things, but it's become an important part of my life. I have the support of my peer navigator, Bill Doss, and our Director, Beverly Nicholson. They are just fabulous people. I've really gotten a lot out of it, and I think others have too.

It helps to be almost 75 years old and still have your wits about you. To realize your experiences in life could be useful for a lot of other people. That's what's working for me. Pg1

Patients Speak: Mr. Michael Dietrich
The Gallium-68 PSMA Scan Experience After Surgery

Mr. Michael Dietrich had the gallium-68 PSMA scan as part of a clinical trial when his PSA starting rising three years after the completion of radiation therapy. He spoke to *Prostatepedia* about the scan and how the results altered his treatment path.

How did you find out you had prostate cancer?

Mr. Michael Dietrich: I had a bad case of prostatitis in 2006. A PSA test done at that time read a value of 6 ng/ml. My urologist was concerned and I had a six-core biopsy performed. All six cores came back negative. I was treated with antibiotics for the prostatitis, which alleviated my symptoms. The urologist thought my elevated PSA was related to the infection and did not stress close monitoring of my PSA. I didn't know any better and I put it out of my mind.

"Though undetected, I probably had prostate cancer at 45 years old when I had that original PSA test and biopsy done."

I had another bout of prostatitis in 2011. A PSA test then revealed a high value of 65 ng/ml. A 12-core biopsy (a newly established standard) was performed and revealed 80% involvement, 4+3=7 Gleason score, and seminal vesicle involvement. I don't know if there is a relationship between my prostatitis and my cancer, but the synchronicity is odd. Either way, the prostatitis led me to my urologist and, weirdly enough, I have to say I'm grateful for it. Gratitude for prostatitis. Weird, huh?

I also was diagnosed with osteoporosis at that time.

I was 50 years old.

Young.

Mr. Dietrich: Yes, pretty young. Though undetected, I probably had prostate cancer at 45 years old when I had that original PSA test and biopsy done. If I had had a 12-core at the time rather than a six-core biopsy, they very well may have found

it then. Needless to say, I'm a fan of 12-core biopsies.

What treatments were suggested to you and which did you choose?

Mr. Dietrich: After the tumor board at Hollings Cancer Center here in Charleston, South Carolina, discussed my case and I was presented all my options, I opted for aggressive radiation and hormone therapy. As I had seminal vesicle involvement, I believed I would need radiation anyway, as I understood typical surgical outcomes involving seminal vesicles were often not so great.

What type of radiation did you get?

Mr. Dietrich: I had both intensity-modulated radiation therapy (IMRT) and brachytherapy. For about six months before treatment, I had androgen deprivation therapy (ADT). I chose to have it a little longer than normal in hopes that it would further shrink the tumors to narrow the target for radiation and further sensitize the cancer to radiation toxicity. I don't know if the wait really helped, but in my mind it made sense. After radiation treatment was finished, I received 18 months of ADT3: Lupron (leuprolide), Casodex (bicalutamide), and Avodart (dutasteride). I've really been very happy with all the treatments I've received.

What kinds of side effects did you have from the radiation and ADT?

Mr. Dietrich: During radiation treatment, I got tired and a little achy. It also constipated me, which surprised me because a more common symptom is diarrhea. I asked for a peristaltic drug as I felt GI motility was an issue, so I was on Reglan (metoclopramide) at the end of treatment and it did help. Currently, I have the extended side effect of having to urinate a couple times a night, but it's tolerable. I have moderate, not severe, erectile dysfunction (ED). I use Viagra (sildenafil) if necessary.

My very fine radiologist is an advocate for the use of rectal balloons during radiation treatment to help protect the colon from unwanted exposure. They were used during every treatment. Having a rectal balloon inserted in your colon (20 plus times) in conjunction with maintaining a full bladder during treatment to minimize organ movement is not a comfortable combination, but yes, it's absolutely worth the beads of sweat you may develop on your brow it if helps with outcome and your future health.

"It was a perception benefit that I'll never forget for the rest of my life."

The hormone therapy had its challenges for sure (like hot flashes, mood swings, and tender nipples), but like any other experience that a life can be presented with, be it negative or positive, I found it a learning experience.

As I was going through hormone therapy, my wife was going through menopause at the same time. We would trade the ceiling fan remote back and forth all night long dealing with our hot flashes. It was a bonding experience and it was interesting to be a guy understanding menopause.

I tried an experiment: from the day I started my hormone injections, I never shaved. I wondered how a lack of testosterone would impact beard growth and, interestingly enough, I had a 5-inch beard after my two-year castrate period. Much of my body hair receded, though.

I lived in a beach town while I was on hormone therapy. If you fully want to understand how testosterone rules an adult male's perception, remove sex hormones from your body, go to the beach, and monitor your perception... and interest. An attractive, half-naked body can be as interesting as a sea gull or a dead horseshoe crab. Interesting, yes. Desirable, not so much.

I was surprised to find, at times, a certain beauty in neutrality and in being in a state of unsexually biased perception. Like the lifting of an obscuring fog to some degree. I was happy when my hormone therapy was over and I got my energy and sexual interest back, but the window of perception was interesting.

I found myself often viewing the world more like when I was a 10-year-old boy. I often experienced lightheartedness and unbiased acceptance of everybody. It was a perception benefit that I'll never forget for the rest of my life. To this day, because of that insight, I am very aware of how hormones currently skew my perception. Aggression, arousal, competitiveness. It's all there, but now subject to more acknowledged objectivity than before I attended eunuch university.

I've not heard that before.

Mr. Dietrich: Really? I am 50. I went to a liberal arts college in the 1970s where there was quite a bit of experimentation with mind-altering substances, myself included. Controversial, I know, but maybe that early use of hallucinatory drugs in my formative years did set a template for accepting/embracing shifts in perception. Maybe, maybe not. Regardless, I would encourage anybody entering hormone therapy

to not be overly wary of it and realize that as your testosterone levels fall, so falls your caring about the fact that your testosterone is going away. Testosterone tends to be very possessive of itself. Be flexible with its passing. Speaking of mind-altering drugs, I was on a low dose of the antidepressant Effexor (venlafaxine) for hot flashes. It cut back hot flashes by 50% and did impact mood as well. It no doubt helped my attitude. Getting off the Effexor (venlafaxine) definitely requires gradual weaning. I missed a dose or two by accident and felt quite nuts. It requires quite a structured commitment, a commitment not to be deviated from.

What did all this do for the cancer control? Did the radiation and ADT keep your prostate cancer in check?

Mr. Dietrich: My hormone therapy ended in 2013. My testosterone came back to my normal (between 700 and 900) and my PSA stabilized between 0.2 and 0.4. Normal readings for a patient who had received radiation, that is. After three years of stability, my PSA started rising mid-2016.

My mother passed away in January of 2016. Right afterward, my PSA started rising. My father passed on as well in December. My parents lived next door to us and we grew incredibly close. Perhaps it was coincidental, but I can't help but wonder if the extreme grief and stress I experienced exacerbated my recurrence and contributed to my short three-month doubling time.

Progressively, my PSA rose beyond 2 plus my nadir of 0.15, signaling likely recurrence in a radiated patient. I had a skeletal CAT scan and an MRI. The bone scan was negative. The MRI was largely negative, but it revealed one—and I can quote—area of enhancement involving the right apex and the right posterolateral mid-gland to base, which could possibly represent residual recurrent disease, and no lymphadenectomy or other metastatic disease to the pelvis.

My oncologist here in Hollings, South Carolina, mentioned the gallium-68 PSMA scan. We found a clinical trial at the University of California, San Francisco (UCSF), which I went ahead and joined.

"We found a clinical trial at the University of California, San Francisco (UCSF)."

You traveled so far to get the scan?

Mr. Dietrich: Yes. I had options somewhere on the East Coast and in Texas, but I chose UCSF because I have friends and family out there.

What was it like to get the scan?

Mr. Dietrich: I had to wait for about a month for a space to become available on the clinical trial. The scan generally costs $4,000, but my insurance covered it.

It wasn't much different than an MRI. Very benign. I was worried about side effects, but I can't say it was any more than with the MRI I had done with a tracer involved. I guess the only thing that really comes to mind is that there was a fairly ominous stainless steel-encased device that shielded the syringe from radiation leakage. I didn't have any side effects from the solution or the scan.

Within days, I communicated with the team performing the scan and they sent me an image and reading. There was one active 3mm node on my right side and a vague, nondescript one on the left, indeterminate but suspicious. No uptake shown on the prostate gland or anywhere else.

What was the plan after imaging?

Mr. Dietrich: That was a process to navigate. Treating oligometastatic disease is controversial with many people feeling that there is no long-term survival benefit in local treatment of local lesions and the correct treatment path is to go on systemic therapy. I was presented with chemotherapy (docetaxel) in conjunction with ADT3. I wasn't ready for that and my gut instinct (or an extreme sense of denial) kept me looking for an alternative.

Having already had radiation to my pelvis, I was wary of further exposure so I looked into lymph node surgery.

I discovered Dr. Jeffrey Karnes at the Mayo Clinic, who regularly performs lymph node dissections on oligometastatic patients.

He performed a biopsy of my prostate and seminal vesicles, which luckily turned out negative on all cores.

On July 12, 2017, I had the lymph node dissection. Twenty-seven lymph nodes were removed. The pathology revealed two active nodes, the very same two nodes that the gallium-68 PSMA scan revealed. I'm in recovery right now from that surgery.

If you compare the gallium-68 PSMA scan to my MRI, the MRI suggested possible local disease in the prostate and nothing in my lymph nodes.

The gallium-68 PSMA scan didn't show anything in the prostate but did show active lymph glands, which was accurate. It was clear. Very clear.

Had I not had that gallium-68 PSMA scan done, it wouldn't have been clear to me what to do. The clarity of the scan and the biopsy made me comfortable with the option of lymph node dissection, which in my situation may offer an up to a 20% chance of durable remission/cure or, if nothing else, may extend my time till I have to consider systemic treatment. A gamble perhaps, but one worth taking I feel, especially as I currently have no gross negative side effects.

How is the recovery going?

Mr. Dietrich: So far, I just have regular incision tenderness and soreness. No infection or anything else.

The gastrointestinal recovery is a slow process. They have to really move your guts around quite a bit and anesthetize your intestines in order to work. Motility and digestive activity take a while to return even if you're not feeling pain. I should probably have waited a couple more days for the flight back home, as it was just a week after surgery.

Do you have any advice for men who are considering getting this scan?

Mr. Dietrich: I wouldn't hesitate. When I compare the results of what my MRI read compared to the clarity of the gallium-68 PSMA scan, it's a no-brainer.

Do you have any thoughts about participating in a clinical trial?

Mr. Dietrich: Well, the gallium trial was just an investigational scan, not a comparative trial involving placebos or a control group. It just felt like any other scan.

As far as my thoughts of seeking treatment options, it can be a frustrating process as you can be presented contradictory beliefs on what's your best path. Keeping focused on current data and talking to several educated oncologists is essential.

Collect data from everywhere, remain objective, and don't stop. Web health message boards can be extremely good sources of both knowledge and support. There are other patients present on boards who are fighting for their lives as well and are very aggressive hounds on collecting and sharing current clinical trial, evidence-based data.

I own a company that services pathology instruments here in the Southeast. I'm always telling my technicians to practice distant objectivity and try to revoke preconceived notions when diagnosing a complicated, failed instrument. Preconceived beliefs can block our subconscious mind from connecting abstract dots into a correct forward path of figuring out a complicated problem.

Beginner's mind?

Mr. Dietrich: Yes, beginner's mind. That's a good way to put it. Be confident. As a patient, you are in a position where you might be more open-minded, motivated, and educated on current data than even some physicians. You are fighting for your life and if you remain open-minded and if you don't have a preconceived belief or a professional position to defend, you can think your way clearly to where you need to go. Pp[1]


XTANDI takes on advanced prostate cancer while you take on what matters to you.
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Talk to your doctor and visit XTANDI.com/info
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Talk to your doctor and visit XTANDI.com/info

Who is XTANDI for? XTANDI is a prescription medicine used to treat men with prostate cancer that no longer responds to a medical or surgical treatment that lowers testosterone and that has spread to other parts of the body. (This is a type of advanced prostate cancer.)

Important Safety Information

Who should not take XTANDI?

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

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

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

How should I take XTANDI?

- XTANDI is four 40 mg capsules taken once daily.
- Take XTANDI exactly as your healthcare provider tells you.
- Take your prescribed dose of XTANDI one time a day, at the same time each day.
- Your healthcare provider may change your dose if needed.
- Do not change or stop taking your prescribed dose of XTANDI without talking with your healthcare provider first.
- XTANDI can be taken with or without food.
- Swallow XTANDI capsules whole. Do not chew, dissolve, or open the capsules.
- If you miss a dose of XTANDI, take your prescribed dose as soon as you remember that day. If you miss your daily dose, take your prescribed dose at your regular time the next day. Do not take more than your prescribed dose of XTANDI in one day.
- If you take too much XTANDI, call your healthcare provider or go to the nearest emergency room right away. You may have an increased risk of seizure if you take too much XTANDI.

What are the possible side effects of XTANDI?

XTANDI may cause serious side effects including:

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

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

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

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

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

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

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QUESTIONS ABOUT XTANDI?

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

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

What is XTANDI®?

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

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

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

How should I take XTANDI?

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- muscle and bone pain
- weight loss
- headache
- high blood pressure
- dizziness
- a feeling that you or things around you are moving or spinning (vertigo)

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

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

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

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

How should I store XTANDI?

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

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

General information about XTANDI.

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

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

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

What are the ingredients in XTANDI?

Active ingredient: enzalutamide

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

Marketed by:

Astellas Pharma US, Inc., Northbrook, IL 60062
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076-1977-PM

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

Revised: October 2016

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