Prostatepedia[1]

[1]expert insight + advice

Imaging

Prostatepedia_October [2019] Volume [5] No. [2]

In this issue....

This month we're talking about imaging for prostate cancer. Imaging technology is advancing rapidly and is transforming both prostate cancer diagnosis and offering new insight into how prostate cancer spreads throughout the body. Less clear, of course, is how these new advances will impact treatment.

Dr. Ammar Chaudry of City of Hope gives us a good overview of the kinds of imaging techniques men are likely to encounter during their prostate cancer journey.

"Imaging technology is advancing rapidly."

Dr. Oliver Sartor breaks down for us the five different types of PET scans available today—how they work, when they're used, the kinds of information they provide, and how their results impact treatment.

Dr. Thomas Hope offers an in-depth analysis of the newest advances in imaging, including PSMA targeted imaging compounds, C-11 Choline, and C-11 ACETATE. He also updates on the progress of UCSF's application to the FDA for the 68Ga-PSMA-11 scan. If that application is approved, in about June 2020, the scan will be available for you at both UCSF and UCLA. That application is unique in the sense that UCSF did not make it proprietary—which means, ultimately, that the 68Ga-PSMA-11 scan may well become readily available to many of you in a few short years.

There are several issues ways that improved imaging might improve the management of prostate cancer. First, the standard imaging techniques used to stage prostate cancer, the bone scan and CT scan, are well known to miss bone and lymph node metastases in many patients. This is part of the reason so many patients progress after initial treatment with surgery orradiation. Improved imaging techniques are likely to do a better job detecting metastases that are currently missed by bone scan and CT scan. This would allow patients with early metastatic disease to receive more effective treatment than local therapy solely directed at the prostate gland.

Second, improved imaging techniques are important to the rapidly evolving treatment of oligometastatic disease. This approach is based on the concept that there are patients who have a limited number of cancer metastases and that treatment of these metastatic deposits with radiation might slow cancer progression or even induce a durable remission. The better we are able to detect the true extent of the metastatic disease, the more effectively the cancer can be targeted.

Charles E. Myers, Jr., MD Pp1

Contents:

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

Contributors:

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

Administrative Offices
PO Box 655, Earlysville, VA 22936

Oliver Sartor, MD
PET Imaging + Prostate Cancer

Dr. Oliver Sartor, the Bernadine Laborde Professor of Cancer Research in the Medicine and Urology Departments of the Tulane School of Medicine, is one of the leading researchers in advanced prostate cancer today. He is also the editor-in-chief of *Clinical Genitourinary Cancer* and the author of more than 300 scientific papers.

Prostatepedia spoke with him about PET imaging and prostate cancer.

Let's start off by talking about PET scans. What are they, and what types are currently available?

Dr. Sartor: Positron emission tomography (PET) scans rely on the positron, which is like a piece of antimatter. When the positron comes out, the opposite of an electron, it interacts with matter in the body. When it collides, it gives off a signal that can be detected by a variety of devices. These PET imaging devices can localize things with great precision using a PET scan. But here's where the confusion begins.

There is a whole variety of PET scans that are dependent on not only the isotope involved but the little carrier molecules that are biologically important, molecules that distribute the isotope in a particular manner so that we can detect a signal.

> *"People talk about PET scans as if there were only one, but there are five different types."*

People talk about PET scans as if there were only one, but there are five different types. There's fluorodeoxyglucose (FDG), Axumin (fluciclovine F 18), sodium fluoride, choline, and prostate-specific membrane antigen (PSMA) PET. People get totally confused about them. Which PET scan are you talking about, and who's going to pay for it?

Right now, there's only one that's reliably paid for, and it's only in recurrent cancer, and that's Axumin (fluciclovine F 18). Everything else is not reliably paid for. For reference, UCLA charged approximately $2,700 for a PSMA PET.

If someone says they're going to get a PET scan for a cancer patient, what they generally mean is a fluorodeoxyglucose (FDG), which is fancy terminology for labeled sugar. The traditional FDG PET uses F-18, which is an isotope of fluorine that will give off a positron. The F-18 is stuck onto a sugar molecule, and it goes wherever the sugar goes in the body. Many parts of the body, such as the heart and brain, are metabolically active under many circumstances, and they will have an uptake of the sugar, which can be detected by the PET scan. This is also true for many cancers. You can trace out a whole variety of cancers by following these little sugar tracers and seeing where they go.

Not all prostate cancer is metabolically active. Others, like lung, esophageal, and testicular cancer can be metabolically active, and the prototype is probably lung cancer, where FDG PET scans are routine.

To the chagrin of many patients and some physicians, FDG PET is not approved for prostate cancer use. In fact, it is specifically excluded. If a doctor orders an FDG PET, it's going to be

hard to have it reimbursed because it's not FDA-approved.

Sodium fluoride PET is another form of scan. A naked fluoride molecule will go into bone and areas of active bony turnover exclusively, so it doesn't go where the cancer goes. The sodium fluoride PET scan doesn't show tumor; it only shows turnover in bone. The turnover in bone can be augmented by the presence of tumor, but it can also be augmented by things like arthritis, inflammation, and almost anything that damages the bone, like a fracture followed by healing. It's like a souped-up bone scan.

A choline PET scan uses a different isotope, including C-13, which has a short half-life. Choline PETs were made famous in the United States through the Mayo Clinic in Rochester because they got FDA approval. Choline PET uses uptake by areas of inflammation, so you can track out the cancer in a more sensitive manner by looking at the choline uptake. They've been able to demonstrate areas of metastasis when conventional imaging fails.

Axumin (fluciclovine F 18) is PET scan that is specifically FDA-approved for use in recurrent prostate cancer. Axumin (fluciclovine F 18) is more sensitive to finding cancer in lymph nodes than CAT or bone scans. There's not a lot of data on the Axumin (fluciclovine F 18) uptake in bone, but it definitely can be taken up in bone.

What has everyone excited is the prostate-specific membrane antigen (PSMA) scan. There's more than one kind of PSMA scan out there, but the one most commonly used is the gallium-68 isotope tracer.

The tracer is a small molecule that will bind to the antigen expressed in a number of prostate cancer cells, but it can be expressed elsewhere as well. If you look at a PSMA scan, there's a lot of uptake in the salivary glands and the lacrimal glands, which are the glands around the eye that make the tears. There's also some uptake in the liver. The typical PSMA scan is a molecule that is excreted into the kidneys. You'll see uptake in the kidneys and then the ureters and the bladder.

There are newer PSMA tracers that are not excreted in the kidney. This could be helpful for viewing the lower pelvis and around the bladder. If the bladder is filled up with isotope, you're not going to see much, but there are new PSMA tracers that can be excreted in the liver instead of the kidneys. The PSMA-1007 can do that.

PSMA tracers used predominantly in Europe include PSMA-11 and PSMA-I&T, and they're both typically bound to gallium-68. Dr. Martin G. Pomper at Johns Hopkins has invented a molecule called DCFPyL that is bound to F-18. It traces out PSMA uptake in accordance with the PSMA distribution tissue in salivary and lacrimal glands, and in the liver, bladder, and kidney. Some people prefer F-18 imaging to gallium-68, but they're both good.

Currently, the PSMA scan is not FDA-approved, but comparative studies indicate that PSMA is more sensitive than choline. UCLA has published that it's definitely more sensitive than Axumin (fluciclovine F 18), which is the current FDA-approved scan.

What does sensitive mean, exactly? Many studies show

that the average patient who is detectable to bone scan probably has a PSA of somewhere between 30 and 70. The PSMA scan is typically positive at a PSA of 0.5. That's about 100 times more sensitive than a bone scan.

"What has everyone excited is the prostate-specific membrane antigen (PSMA) scan."

CAT scans and MRI depend on cross-sectional imaging. If you're going to define something on a CAT scan or an MRI, it typically needs to be about a centimeter in size. People argue about the number of tumor cells present in a centimeter of tumor, but it might approach a billion cells in one centimeter of tumor. On a CAT scan or MRI, you're waiting until you get a billion cells in one spot before you detect anything. The PSMA is probably about 50 times more sensitive than CT or bone scan, or better.

How does this change treatment?

Dr. Sartor: The reason we're interested in finding small tumors is that you want to know *if* the cancer has spread and *where* it has spread. The success of almost any local therapy, such as surgery or radiation, depends on knowing the location of the cancer. So, different scans might alter your treatment plan. Studies have shown that PSMA detects more cancer than previously suspected. For example, imagine a patient with Gleason 8 and PSA 20 who has a small nodule on their prostate, and so they're clinical-stage T3A. We know that if we treat these patients with surgery, the probability of their failing could be around 50% depending on how many biopsies are positive. The surgery hasn't failed if the cancer has already spread by the time we do the surgery. It's the imaging that failed.

If you get a PSMA scan, you might be able to avoid non-curative surgery. I hesitate to say "unnecessary" because surgery might have a positive effect. But surgery here is noncurative because you have to do something more. The same is true for radiation. And if you're using a focal class of therapy, you want to know where the cancer is in the best possible way.

We don't have all the scan data that we need. Most of the Axumin (fluciclovine F 18), choline, and PSMA scans are done for patients who are recurring after initial definitive therapies. These are patients whose PSAs are rising after surgery or radiation, and that's where most of the data originates from now.

We can use specialized radiation techniques such as stereotactic ablative radiotherapy (SABR) or stereotactic body radiotherapy (SBRT) to delay rising PSA after treatment. There's some data from a prospective randomized trial by Dr. Peter Ost in Belgium [*Prostatepedia* spoke with Dr. Ost in February, 2018] that shows that SABR/SBRT can delay the time to PSA progression. Folks at various centers have shown that, depending on what you radiate at the time of recurrence, if there's one or more lesions, and where they're located, about 30% of patients might have a complete remission of PSA after radiation on PSMA-detected scanning.

Based on several data sets, we typically find that, for those with PSA between 0.5 and 1.0, are about 60% positive on a PSMA PET. Lower than 0.5 PSA, only a minority of scans are positive. Above 1.0 PSA, the vast majority are positive. PSMA is probably a little better in the lymph nodes as compared to the bone, but there's a lot more work that needs to be done regarding localization.

The bottom line is that PSMA scans are the most sensitive current technology for finding cancer. They seem particularly helpful for cancer in the lymph nodes, and for those who have recurrent cancer because treatment plans depend upon the location of the tumor, as determined by scans.

The VISION trial is about to complete accrual in September, 2019. It's a Phase III trial of PSMA-617 with lutetium-177 for the treatment of advanced prostate cancer. This is a prospective randomized trial, now closed to accrual, so you can't pursue it at this point. But it's an important trial that will look at whether or not PSMA lutetium-177 prolongs radiographic progression-free survival or overall survival in patients who've been pre-treated with things like Zytiga (abiraterone), Xtandi (enzalutamide), and Taxotere (docetaxel). It'll probably take about a year to report. Pp1

Thomas Hope, MD
The Future of Prostate Cancer Imaging

Dr. Thomas Hope, MD, of UCSF and the San Francisco Veterans Affairs Medical Center, is keenly interested in novel imaging agents and therapies for prostate cancer and neuroendocrine tumors.

Prostatepedia spoke to him about the future of imaging for prostate cancer.

What do you consider the most promising advances in imaging in the last few years?

Dr. Hope: In imaging of prostate cancer, the main development is the family of PSMA targeted imaging compounds. There are many different positron emission tomography (PET) radiotracers used today for imaging. They let us know where disease is located in the body, and they are used particularly in patients where there is a concern for metastatic prostate cancer. In the last few years, radioligand therapy has been used to target and treat disease in patients with metastatic disease.

The agents that were in development two years ago are still the main ones being evaluated today. Overall in imaging, the main thrust has been to get these PSMA-targeted agents into clinic as soon as possible. But we're getting much closer to FDA approval and widespread use.

What is radiopharmaceutical imaging, and how is it used in prostate cancer?

Dr. Hope: A radionuclide is a radioactive atom such as gallium-68 or fluorine-18. These atoms decay, giving off radiation. Certain radionuclides can be used to *image* patients and certain radionuclides can be used to *treat* patients. We attach radionuclides to radioligands.

A radioligand is, a protein or molecule that attaches to a radionuclide and carries it to a target within a cancer cell or other cells. They're not only used for imaging of cancer, but also for treatment. That is what people refer to as molecular imaging or radiopharmaceutical imaging.

How does positron emission tomography/computed tomography (PET/CT) work?

Dr. Hope: Some radioactive atoms called radionuclides decay by emitting a positron. This positron decays by giving off two photons. These photons are unique in that they go in exactly opposite directions. The two photons create a line, and if we can detect those two photons, we know where the origination of the decay occurred. This is how PET imaging works. And given how complicated the technology, it's amazing to think how many thousands of times per day PET/CT is used across the world.

PET images the decay of the radioactivity that's attached to these small proteins, using a special device called a PET detector. A lot of advancements have been made with PET technology that allow us to see better and smaller amounts of activity within the human body. PET imaging allows us to detect a certain type of radiation that we target to tumors in patients, whether in cancers or in other areas, such as the brain or heart.

Then we attach that special detector that images the PET radioligand to a CT scanner. A CT scanner sends radiation through the patient and makes a map of the density inside their body. That allows us to obtain anatomic images. A PET/CT is the combination of a PET scanner with a CT scanner, directly adjacent to each other, so that we can merge the images together.

How does PSMA come into this?

Dr. Hope: Prostate-specific membrane antigen (PSMA) is a protein that's overexpressed mainly on prostate cancer cell surfaces. Today, we have radioligands that bind to PSMA. The term PSMA describes both the imaging agents that bind to the protein PSMA and to the target of the agents on the cancer cell.

That's very confusing!

Dr. Hope: Yes, it is. And there's a whole family of these PSMA-targeted compounds. For example, F18-DCFPyL is in Phase III trials. There's 68Ga-PSMA-11, which we're working on at UCSF. There is fluorine-18 (18F-PSMA-1007). There are hundreds of these different compounds. 177Lu-PSMA-617 is one that is labeled with lutetium-177, and is currently in Phase III trials for treatment of metastatic prostate cancer. They all are similar, and they target the same protein.

The take-home point is that this small molecule binds to a radioactive radionuclide, which can be gallium-68, fluorine-18, or lutetium-177, and it carries that radiation into the cancer cell by binding to the PSMA molecule on the surface of the cell.

Last time we talked, UCSF was gathering information to apply for the new drug application (NDA) for PSMA-11 with the FDA. Where are you in that process, and how soon will PSMA-11 be available to patients at UCSF?

Dr. Hope: It was quite a task, but we successfully submitted the NDA to the FDA a couple of weeks ago. It'll probably be about nine months before the FDA has decided whether to approve the drug. We're optimistic that the FDA will agree to approve 68Ga-PSMA-11.

UCSF worked with UCLA to complete the NDA, which was a wonderful and productive collaboration. When you're talking about academic institutions that don't have departments of people who write NDAs, it was helpful to have extra bandwidth and people working together to make it happen. A lot of work goes into writing an NDA like this. I can't say enough to thank UCLA for agreeing to embark upon this path with us.

If our NDA gets approved in nine months, it will then become available for patients at two institutions: UCSF and UCLA. Our two institutions certainly can't image every patient in the United States who needs this imaging study. But for a short period of time, availability will be limited to these two institutions.

You said it's not the normal process for an academic institution to do this. What prompted UCSF to take that step, and what does it mean for patients in the long run?

Dr. Hope: Why did we do it? I ask myself that same question. Why did I spend the last year doing this? I'm a radiologist, an academic, and a nuclear medicine physician. We run clinical trials all the time, and we write papers. The vast majority of what we do, in the end, does not change much for the patient. So, it has always been appealing to me to not just publish our research, but to make our research available to patients. This would change the practice of how patients with prostate are imaged and treated. The idea that we could do something more than what we typically do is motivating.

Also, I give a lot of credit to the FDA. They have been incredibly supportive and made us believe that we could do it. Ten years ago, no one would have believed that an academic institution could have written an NDA; it would have been laughable. Even people at my own institution did not take us seriously at first. But the FDA was supportive and kept asking us when the NDA was coming, checking up on us, and telling us they wanted us to get the NDA done. It's an unusual circumstance, and it probably won't happen many more times.

We decided not to make PSMA-11 proprietary, which is what makes this NDA unique. We put in all this work, but instead of paying the fees to make it our own, which would mean that we would own and sell it, we made it non-proprietary. Now, anyone at any institution or company can submit paperwork to make the drug themselves. It will take time for a number of these institutions to open up their sites and provide 68Ga-PSMA-11. There are a few paths to that.

Other academic sites could submit their own NDAs. Larger prostate centers will probably do that.

Companies will make small kits, which we call "shake-and-bake kits." You add the gallium to a vial, you "shake" it up, and the gallium labels to the compound. Then you

can use it to image a patient. There are many companies that make these kits, and they can reference our NDA to hopefully quickly obtain approval.

Finally, radiopharmaceutical distributors are large companies that have cyclotrons and other radiopharmacies around the country that already distribute radiopharmaceuticals. Those companies can also submit paperwork to make this drug at their sites and distribute them to local hospitals.

Your NDA is like a gateway.

Dr. Hope: I hope so. It starts the process.

That's an innovative approach. You've got through all this work, and now it's not proprietary.

Dr. Hope: I think of this as a crowdfunded process. This study is unique in that we didn't have any funding from grants, NIH, or any organization. This was nearly fully paid from insurance companies and patients who paid for the studies. We billed patients for the radiotracer, and we billed insurance companies for the PET portion, including the technical fees. The patients who wanted this for their own clinical care created the foundation for the approval of this drug. That's never been the case before.

Disruptive, to use a term that they throw around a lot here in the Bay area.

Dr. Hope: Yes, disruptive is true to a certain extent, except I don't think this is reproduceable. It's a unique circumstance that PSMA-11 was not patented, and no one was developing it. It needed someone to take it across the finish line. That doesn't happen often. Most of these drugs are owned by companies, and we can't just run trials on them. This was a very unusual circumstance.

What are some of the other common imaging techniques?

Dr. Hope: C-11 choline was the first of these agents to be approved by the FDA in 2012. It was approved by the Mayo Clinic, and the first academically sponsored NDA ever approved. It's an amino acid that's used in the cell membranes of tumor cells, and it gets taken up as non-specific, so other cancers will take up choline. There are some benefits and negatives with C-11 choline. It works reasonably well, though it's limited in patients with low PSA. Early on in their recurrence, it has some limited detectability.

The main negative is C-11 has a 20-minute half-life, and so one needs a cyclotron right next to your PET/CT in order to do this study. Only sites that have cyclotrons can make this agent and use it clinically, so radiopharmaceutical distributors aren't able to distribute C-11 choline. It didn't become widely available quickly. For about four years, it was only available at the Mayo Clinic.

Axumin (fluciclovine F 18) is fluorinated. It's labeled by F18, and it has a 109-minute half-life, so it's much longer. A central radiopharmacy can make it and distribute it within a three-hour radius. For example, we use Axumin (fluciclovine F 18) at UCSF, and we order it from a radiopharmacy in Oakland.

They send it to us in a car, and we inject patients. Axumin (fluciclovine F 18) is much more widely available than C-11 choline, and it was quickly available because it was developed by a company who had a contract in place with a radiopharmacy that could distribute it nationwide.

The detection rate of Axumin (fluciclovine F 18) is similar to C-11 choline. It is limited also in patients with low PSAs in particular. It's better than conventional imaging, meaning CT or MRI, but it has a low detection rate in patients with a PSA of less than 2.0.

There are great benefits to Axumin (fluciclovine F 18). When it came out, it was the only thing available in many parts of the country, and it still is. Axumin (fluciclovine F 18) is the most commonly used imaging agent as the standard-of-care imaging agent for patients in the United States who have or are at risk for metastatic prostate cancer.

What is C-11 acetate? How does it work? How does it compare to the other imaging agents?

Dr. Hope: Acetate is another radiotracer. It's labeled C-11, and it's not distributable. It has been studied less than choline, Axumin (fluciclovine F 18), and PSMA, so there's not a ton of data on it. Because no one has done a good job describing it, and because it has not been published well, we do not use it. One paper out of a group in Arizona showed reasonably good detection rates overall. It's hard to tell.

To run these studies properly, we need blinded readers to look at the study separately, correlate the pathology, and determine

the sensitivity and specificity, all in a controlled manner. Writing a paper retrospectively with one reader giving a detection rate overestimates detection rates. This makes it difficult to tell what the actual benefit is in those patients.

What is lutetium-177, and how does it work?

Dr. Hope: PSMA-617 is a radioligand, a small molecule that binds to a radioactive radionuclide. It can be labeled with gallium-68 for imaging, or it can be labeled with lutetium-177 to treat patients.

Lutetium-177 decays by emitting an electron, and this electron causes DNA damage in about a 1-millimeter radius sphere around where the radiation is deposited. You need about 1,000 electrons to traverse a tumor cell in order to cause that tumor cell to die, and so if you can get enough lutetium into a tumor cell, you can subsequently kill the tumor. That's the idea behind radioligand therapy, using a radioligand to target a tumor cell, carry the lutetium into it, and having the lutetium decay, causing DNA damage in the cell, hopefully subsequently killing it.

This was studied in Europe on a compassionate-use basis and not in a trial setting. The initial data that came out of Europe was positive. Subsequently, an Australian group performed a prospective, single-arm Phase II study that recapitulated the results seen in Europe. After that, a company named Endocyte bought the rights to PSMA-617 and started a Phase III trial, and Endocyte has since been bought by Novartis. The trial is called VISION and focuses on patients with castrate-resistant prostate cancer who are after one line of chemotherapy and either abiraterone or enzalutamide. It is near completion of enrollment. When that trial closes enrollment, they will wait for their data to mature and, hopefully, they will get FDA approval in one to two years.

Overall, it's an effective treatment. In maybe half of all patients treated with this drug, their PSA will fall, but it's very durable. Once we stop administering the drug, patients' PSAs will rise again. One of the big issues in the community is how to improve the durability of PSMA-617 labeled with lutetium to improve patient outcomes.

What are some of the theories on how you're going to improve durability?

Dr. Hope: We're focused on many ways to improve durability. For example, we have a clinical trial combining PSMA-617 with immunotherapy Keytruda (pembrolizumab) plus lutetium-177Lu-PSMA-617. The idea is that immunotherapy can improve durability, and we can incite the immune response by administering radiation that causes DNA damage.

People are thinking also about different types of radionuclides. We want to use actinium versus lutetium. How do we improve the timing and frequency of administrating the drug? Do we want to do it every six weeks or space them out differently? There are many different approaches. Right now, the trial is going to define the use of the drug as 200 millicuries every 6 weeks for 4 to 6 cycles.

How can patients enroll in this trial? Are there any other trials that should be on patients' radars?

Dr. Hope: We have started the 68Ga-PSMA-11 imaging trial. If you want to enroll in that, you should email psma@ucsf.edu. Our clinical research coordinators will contact patients, see if you qualify, and set you up for having the study performed.

In addition to other imaging trials, we have four therapy trials. One is the lutetium-177Lu-PSMA-617 plus Keytruda (pembrolizumab) study. We have a Phase I trial of a completely novel lutetium-labeled PSMA-targeted therapy that's currently in its dose-escalation cohort. I'm not sure if patients would be interested in that unless they're at UCSF. We have another Phase I trial of another lutetium-labeled PSMA radioligand therapy. All these trials are still research, and nothing is FDA-approved yet.

How are the imaging techniques we've discussed changing patient care? Is it a revolution in which you don't know what to do with all the information that you're generating?

Dr. Hope: We've published literature looking at the impact on management. What generally happens is that patients who have no evidence of metastatic disease but have biochemical recurrence will have oligometastatic disease. That means that a few sites of disease are detected. They will often get tumor-targeted radiation, in which we aim external beam radiation at those few sites of disease. A large number of patients will convert from either active surveillance, when we watch the PSA rise until you get metastases, or androgen deprivation therapy (ADT) to getting metastasis-targeted therapy. Some patients who are getting radiation therapy and have widespread metastases on PSMA-PET will go from targeted therapy to ADT or systemic therapy.

These changes in management occur at a fairly high rate. Over 50% of patients have a major change in management, which means going from systemic therapy to targeted therapy or targeted therapy to systemic therapy.

So, patients are having their management changed dramatically based on the results of these imaging studies. At the same time, we have no clinical data to tell us whether or not that's the right decision. We all assume it is. It makes academic sense, but we don't have any large randomized trials. We don't have anything to show us that the management change based on PSMA-PET results is appropriate.

Is that just something that we need to grapple with? We don't really understand what the information means and how to change? What should be done?

Dr. Hope: It's a problem that PSMA-PET clearly works better than everything else. The oncologists and the surgeons all believe that. Once PSMA-PET becomes FDA-approved, then what patient will agree to be randomized to perhaps not getting PSMA-PET? No one would.

Even now, most patients don't want a randomized event, even before it's FDA approved, so we're in a place already where it's nearly impossible to run a randomized trial to demonstrate the correct management change based on PSMA-PET.
A good trial is being run out of UCLA randomizing patients with a low PSA after radical prostatectomy to either getting a PSMA-PET or getting standard-of-care imaging. The goal of that is to show that the PSMA-targeted radiation therapy will improve patient outcomes. Half of the total 200 patients are enrolled. It's important that this trial complete before PSMA-PET gets FDA-approved.

Right now, randomized trials are the gold standard. Could you see a future in which that is not the case?

Dr. Hope: Randomized trials are not going to get replaced. There are many different trial designs. After the UCLA trial is done, no one will want to be randomized to PSMA-PET or none. Once PSMA-PET is widely available, then you need to change the way you think about your trial design.

Instead of randomizing to getting it or not getting it, you get the PSMA-PET, and then we randomize the type of treatment based on it. For a example, one could do metastasis-targeted therapy versus metastasis-targeted therapy plus six months of ADT. We need to know which types of treatments to combine and to understand the right approach for different types of patients based on PSMA-PET results.

There is a huge need to have a trial that shows that molecular imaging improves patient outcomes. Pp

Ammar Chaudhry, MD
Imaging + Prostate Cancer

Dr. Ammar Ahmed Chaudhry, a diagnostic radiologist, is an Assistant Clinical Professor in the Department of Diagnostic Radiology at City of Hope in Duarte, California.

He spoke with *Prostatepedia* about imaging for prostate cancer.

Why did you become a doctor?

Dr. Ammar Chaudhry:
My experiences with both of my parents being ill motivated me to become a doctor. When I was eight, my dad had a heart attack, and we had no idea why people got heart attacks or what was going to happen. The doctors told us it was a blockage in the LAD, but we didn't know what that meant. We didn't even know what LAD was. There was no Wikipedia, so you can imagine how we scrambled for information. We came across some old encyclopedia, and it said that LAD blockage was called the "widow maker" because it caused sudden cardiac arrest, and people usually die from it.

Reading all that information got me interested in two things. First, I was interested in seeing how the body reacts to different stresses and how those stressors could lead to heart attack, cancer or another disease. Second, I knew that I wanted to help others like my family – people who don't know what the diagnosis means or what to do after a diagnosis.

"It is not uncommon for patients to read their reports and feel anxious about the findings."

The physicians saved my dad's life, and they brought comfort to the family. I immediately thought this is a great profession and that was the moment I decided to become a doctor.

In 1997, my mom had a chronic cough. First, they thought it was sinusitis or post-nasal drip. Then, they thought it was something else. After a few months of different tests, she got a CT scan, and they said it was scleroderma causing pulmonary fibrosis.

By then, we had a computer and the encyclopedia, Encarta, so we learned that scleroderma was an autoimmune condition. Because the diagnosis was delayed, she missed out on some of the therapy she could have gotten had it been detected earlier. At that time, they thought the only thing that would save her life was a lung transplant.

There are no diagnostic imaging biomarkers that indicate which treatments will work or not for a patient. Because of this, our healthcare system is set up with steps: first you do this, then this, and if those don't work, then you get a transplant. Invariably, most patients have a mixed response. There are some benefits to treatments, but some areas of the lungs get better, some get worse, and some stay the same.

That cycle continued for about a decade for my mother, and by the time she got to the third treatment, they said she was too sick, and was outside the transplant window. Unfortunately, she passed away.

I was in medical school at the time, and this inspired me to improve diagnostic imaging. Had they detected my mom's lung disease and my father's heart disease earlier, they wouldn't have suffered through a lot of the complications of these diseases. That's what got me into medicine and then radiology.

Today, my research focuses on early detection and identifying imaging biomarkers that can predict response. That's an area of huge unmet need.

Once someone is diagnosed with prostate cancer, they want to know their treatment plan. How do they decide which treatment to get, if any? We need to know if imaging can make the therapeutic regimen specific for the patient, and not just a general plan for the whole population. I'm focusing on this in different cancer subtypes.

Your experiences probably make you sensitive to the kinds of experiences that your patients go through.

Dr. Chaudhry: Yes, exactly.
Every time I interact with patients, these questions come up. Before coming to City of Hope, I was at Johns Hopkins working with patients who had brain tumors. We wanted to identify areas of the brain that control certain functions, such as the brain centers that control hands, feet, or language.

Traditionally, doctors would open up the skull, place electrodes on the brain, and use direct brain electrical stimulation to identify different control centers for language, motor function, vision, etc. It was invasive and time-consuming.

I wanted to know how we could make that better for patients,

so I started the functional magnetic resonance imaging (fMRI) program here at City of Hope for presurgical brain mapping.

We do our presurgical brain mapping noninvasively. Patients come here for their regular brain MRI, but in addition to identifying the tumor, we also identify functional areas of the brain and correlate them to a hard-end reference of the tumor's location. This helps to plan which surgical technique to use, reduces the craniotomy size, and helps preserve functional areas of the brain.

Before I examine a patient, we talk about why we're doing certain things. It inspires me to do better. The whole exam takes about an hour or so, and patients understandably are nervous about the tumor.

That's the focus of my research right now. The standard-of-care right now is task-based functional imaging, where the patient follows commands, and we use that to identify the brain control centers in about an hour. What we do in these new techniques takes about eight minutes as we identify the control centers without the patient doing anything.

We recently published a paper that successfully identifies the language area of the brain. We got a few awards in the past several years related to this work, so I'm proud of that.

What kinds of imaging are patients with prostate cancer likely to encounter along the prostate cancer journey?

Dr. Chaudhry: For example, let's start with standard care for a screening patient. We're concerned about a lesion on a 55-year-old man during the prostate exam. We check the PSA. If the PSA is high enough, he'll get a prostate MRI because it has the best soft tissue resolution. We will look at the prostate gland to find the lesion.

"In each patient's life, family, parents, kids, jobs, and insurance coverages also affect treatment decisions and stress."

We can also perform functional techniques such as diffusion-weighted MRI. The prostate has a high water content that moves freely in the gland. Tumors scar down the gland and limit water motion. Diffusion is just a simple principle of chemistry meaning that things move through a medium randomly. That's true inside or outside of the body, unless something restricts that free motion.

Prostate tumors restrict water motion, generally. If you read the MRI report, and it says that we found a 5-millimeter lesion with a restricted diffusion, that means there's a lesion that is limiting water movement. This is highly concerning for prostate cancer.

Once we've identified that, then we do a staging. We identify areas in and around the prostate to see if the tumor has metastasized to a nearby lymph node, liver, or most commonly, bone.

At that point, we'll do a bone scan, or single-photon emission computed tomography (SPECT-CT). Our bone has a lot of phosphate, which is one of the common ions that calcium binds to and gives us bone marrow density. We tag a radioactive diagnostic agent, called technetium, with a phosphate analog, and this circulates through the body. Tumors that cause high bone turnover have preferential increase uptake of this imaging agent in an area of the tumor relative to normal bone. That's how a bone scan picks up bone metastases.

There are other normal causes of increased bone uptake, however, which look like several dots on the scan. The most common in a 55-year-old is arthritis in the knees, spine, and shoulder. Because many patients ask to review the images, you should know that just because you see what looks like 20 lesions, you shouldn't be alarmed. I don't like the term lesions; I prefer foci. If you see multiple foci of increased uptake, that just means you have to put that in context of location.

If the PSA is normal, and the patient has no symptoms, then that area of uptake is probably related to arthritis. The patient may have also had a traumatic fall. Perhaps you slipped down the stairs, had a skiing accident, or fractured a couple of ribs. Initially, you'll get that transient pain in the first week during the fracture, and then the pain subsides. But the bone repair process takes a few months to a year to fully complete.

Do patients frequently look at these imaging results and panic because they think that there's cancer?

Dr. Chaudhry: It is not uncommon for patients to read their reports and feel anxious about the findings. It is important to note that all of the findings are not necessarily cancer. Imaging findings are interpreted in context of clinical findings. That's usually when I get involved, and I speak with our GU team, whether it's Dr. Clayton Lau (the surgeon), Dr. Tanya Dorff (the medical oncologist), or Dr. Sumanta Pal (the medical oncologist), to explain that the areas with increased uptake are benign because they're due to arthritis or some other inflammatory process. This shouldn't stop anyone from getting a second opinion; I just don't want patients to stress because stress is generally not good.

Patients take things differently. The other day, I did an fMRI on a patient's brain who was more worried about the implications of her treatment on her husband and kids than herself.

In each patient's life, family, parents, kids, jobs, and insurance coverages also affect treatment decisions and stress. There are so many factors, so I'm all for patients getting a second opinion. But you shouldn't fret. Take everything you read with a grain of salt. Don't make rash judgements based on any one single data element.

What kinds of readings would a bone scan show?

Bone scan is used to assess spread of prostate cancer to the

bones. If a bone scan comes back negative and PSA is elevated, the patient will get a whole-body contrast-enhanced CT scan that evaluates for metastatic lesions in the thorax (e.g. lung, lymph nodes) or abdomen or pelvis (liver and other lymph nodes). Usually, lesions in the lungs, liver and lymph nodes do not show up on a bone scan.

"Adding more imaging may not necessarily add more value."

What are the big developments in imaging today?

Dr. Chaudhry: New imaging sizes are being developed, and that will change patient care in the upcoming months. There are also two big changes.

One is in PET scans. Positron emission tomography (PET) scans have been in clinical practice for over 20 years, so it's not new technology per se, but there's been a lot of development in radiotracers.

For PET scans, we conventionally use a glucose analog tracer. We take glucose and we label it with a radioactive fluorine, which is called a fluorodeoxyglucose FDG PET scan. We use glucose for metabolism because cancer has an increased metabolism. In theory, we can pick up aggressive cancers with an FDG PET scan, and it's good for aggressive prostate cancer, even if it's less than a centimeter.

However, not all forms of prostate cancers are aggressive. Cancers with a low level of metabolic activity are considered indolent, and they blend in with the normal prostate gland, so it's difficult to pick them up.

Over the last decade or so, there has been a lot of work done to develop two new agents. Axumin (fluciclovine F 18), which is FDA approved to detect prostate cancer, is a choline analog. Choline is a metabolite that increases in prostate cancer relative to normal prostate tissue. On FDG PET CT, choline lights up. It is sensitive, but for sub-centimeter lesions, it is still mixed. It is better than FDG, but in a tumor of less than a centimeter, it is 50/50.

That led to the next generation of prostate biomarker, the prostate-specific membrane antigen (PSMA). All prostate cancers have increased expression of PSMA. Over the last half-decade, there has been a lot of work done at NCI cancer centers with the agent and it recently completed a Phase III trial. It will probably get FDA approval over the next 12 months and be used as the standard-of-care for imaging in prostate cancer diagnosis. PSMA does a good job at detecting the sub-centimeter lesion, and it's more sensitive to indolent, early stage cancers. We recently got FDA approval to use this imaging agent at City of Hope for our prostate cancer patients. My goal is to detect cancer early because early detection improves overall survival.

A lot of patients in our network travel for imaging studies, particularly to Europe or other locations within the United States. Sometimes, they pay for these out-of-pocket. What are your thoughts for men doing this, and do you have any advice for them?

Dr. Chaudhry: I'm biased because I'm in imaging, so I am not going to say no to better imaging. If someone wants to get a PSMA PET scan for early detection purposes, I would definitely support that. Make sure it's safe, especially if you're going to travel.

"I urge patients with high concern or suspicion of prostate cancer to go to facilities like City of Hope to identify their cancer."

If you're traveling for a Phase I study, which is drug safety-based, so it's not looking for efficacy, then the benefit is questionable. If they don't see anything, then it's an individual choice. Some people will treat you the same if you have 20 lesions or 3; you're still going to get systemic therapy.

Adding more imaging may not necessarily add more value, but if you know something like PSMA PET, for example, is offered in Europe or City of Hope, and you want to travel for that, I would definitely encourage it because it's already been shown in good, published literature that it's safe and effective.

Any advice about imaging for prostate cancer for the men reading this?

Dr. Chaudhry: I would highly advise those diagnosed with prostate cancer to go to areas that specialize in cancer care because we have invested so much to make sure we offer the best. For example, we invested $30 million this year in new equipment for imaging because we care about finding cancer early (e.g. less than a centimeter). All our staff is highly trained and specialized from scan acquisition to scan interpretation to the tumor board. That's one circle, a complete feedback loop. The PSMA PET or diffusion imaging that we provide to our patients is not available at your average imaging facility.

If you have an aggressive family history, your PSA is high, and your doctors can't find any cancer, I would highly recommend that you go to a specialized place. Patients in that situation definitely need to come to a place like City of Hope to make sure the cancer is found, especially if it's localized in the prostate bed. That's the ideal scenario because surgery is curative at that stage.

If you are imaged by an old scanner that cannot do advanced imaging of the prostate, then it will not pick up a five-millimeter lesion. Most cancers double in three months, but what if the cancer quadruples in size or metastasizes to the liver? Because of poor or old imaging technology, you've gone from a curable patient to dealing with the consequences of metastatic disease.

I urge patients with high concern or suspicion of prostate cancer to go to facilities like City of Hope to identify their cancer.

Choosing between facilities like City of Hope and The University of Texas MD Anderson is a longer, more complex discussion. But I would definitely urge you to go to an NCI-designated site because that can make the difference between a curative staging and Pandora's box. Po!

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

Coming Up!

November:

Bone + Prostate Cancer