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SPECIAL ISSUE · 10.2022

SOMEWHERE IN THE MIDDLE

PROSTATE CANCER IN THE OLIGOMETASTATIC SETTING — WHEN IT HAS NOT FULLY METASTASIZED — CAN NOW BE DETECTED AND TREATED EARLIER, IMPROVING SURVIVAL RATES.

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TIME TO HIIT IT!
HIIT workouts may help patients with prostate cancer who are on active surveillance.

WINEMAKING FOR A CAUSE
One patient with prostate cancer is using his love of winemaking to give back.

SOMETHING OLD, SOMETHING NEW
Researchers are finding new ways to use older drugs to treat bladder cancer.

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20 YEARS OF GAME-CHANGING ADVANCES
The past two decades have brought drastic changes in the kidney cancer space.

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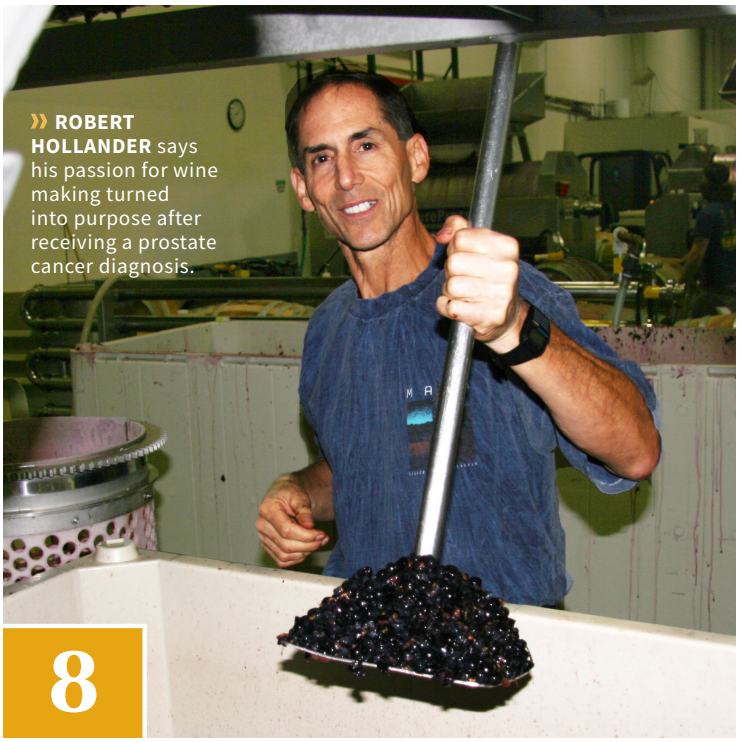
A step-by-step guide to start HIIT workouts.



» **ROBERT HOLLANDER** says his passion for wine making turned into purpose after receiving a prostate cancer diagnosis.

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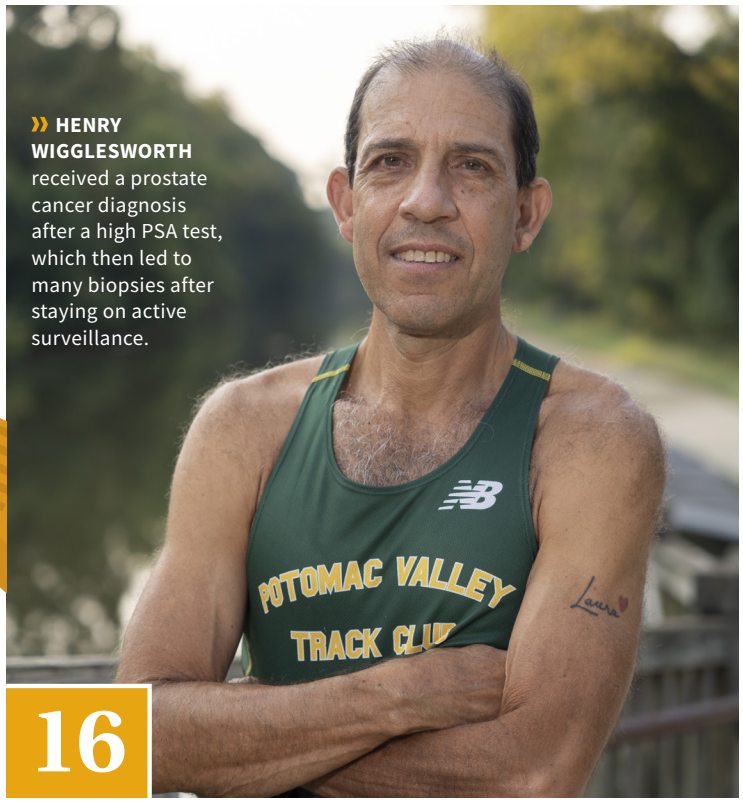

» **HENRY WIGGLESWORTH** received a prostate cancer diagnosis after a high PSA test, which then led to many biopsies after staying on active surveillance.

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publisher's note

A Revolutionary 20 Years in Kidney Cancer

METASTATIC KIDNEY CANCER WAS once seen as a malignancy that was resistant to typical cancer treatments such as chemotherapy and radiation, leaving patients with limited options and low life expectancy. However, the past 20 years have brought great advancements and approvals to the space, improving life expectancy and quality of life.

As *CURE*® continues to celebrate its 20th anniversary, we spoke with two experts in the kidney cancer field about treatment discoveries. Both agreed that the greatest advancement in the past 20 years was targeted therapy. And since 2005, there have been more than a dozen Food and Drug Administration approvals for metastatic kidney cancer, which demonstrates how significant these treatments are for patients.

Along the way, treatments have significantly improved not only survival but also quality of life. One expert noted that treatment 20 years ago resulted in patients consistently having flu-like symptoms, and many eventually stopped treatment because of it. With these new treatments, side effects still occur, but they are much more manageable and do not affect quality of life to the point of stopping treatment.

Also in this issue, Robert Hollander discusses how he turned his passion into purpose. As a lover of wine for many years, he began making his own for fun, but that all changed after he received a diagnosis of metastatic prostate cancer. He started a foundation and is now funding research for prostate cancer with the sales of his wine. It became a great way of dealing with his situation and continuing his passion while also helping a meaningful cause. "Everybody who goes through this journey has to find a way of dealing with a difficult situation," he says. "The winemaking is fun, and having people enjoy it is great too. It's a small thing, but (I'm) just trying to (make) the best of a challenging situation."

And don't forget to HIIT it! For some patients with prostate cancer, treatment with standard therapies may not be the best course, so their doctors recommend active surveillance. However, this period of time can be difficult for many patients, causing psychological distress and affecting their quality of life. But new data demonstrate that high-intensity interval training (HIIT) workouts can improve these patients' quality of life. *CURE*® spoke with an expert about how patients can start a HIIT program and the benefits they may get from it.

As always, we hope you find these stories to be informative and inspiring. Thank you for reading.

MIKE HENNESSY JR.
President & CEO
MJH LIFE SCIENCES®

Advances in Imaging Lead to Earlier Treatment

MANY PEOPLE KNOW OF only two states of cancer: local (in one part of the body) or metastatic (when the cancer has spread to other parts of the body). However, there is another state of disease that is somewhere in the middle, a state that is featured in this issue of *CURE*®. Most types of cancers, including prostate cancer, are managed based on their stage, which is a way to quantitatively describe in what locations of the body cancer has been found. This is usually the first step after an initial diagnosis from a biopsy. Imaging scans and other tests might reveal early-stage cancer, which is typically localized to the organ of origin and surrounding tissues or lymph nodes. Or it could be termed advanced or metastatic cancer. In the case of prostate cancer, this would be exemplified by its spreading to bone. The most important distinction between early-stage and advanced-stage cancers is long-term curability.

The term "oligometastatic," which is the state somewhere in the middle, was first proposed for prostate cancer in 1995. It encompasses a few isolated metastases. The intriguing aspect of this designation is discovering whether long-term cures can be accomplished. In the past few decades, there have been significant improvements in medical therapies as well as focused radiation and other local therapies that might help reach that goal.

Additionally, more precise imaging such as prostate-specific membrane antigen (PSMA) PET imaging has helped doctors diagnose metastases earlier than through a regular work-up, meaning patients can be treated even earlier. One patient featured in our story benefited from imaging such as this. He, a retired urologist, said that the metastases probably would not have been detected with a regular work-up. Prior to his PSMA PET scan, which detected his lesions, standard imaging had detected no lesions.

Many more milestones need to be reached before oligometastatic prostate cancer and other malignancies can be managed with curative intent as a standard of care, especially because this approach adds side effects and expenses. This is where well-designed clinical trials come in. These are ongoing and use the most appropriate and up-to-date imaging, localized and systemic treatments to compare them with our current treatment approaches. The component usually being tested is localized radiation or surgery applied to the oligometastatic sites. Ultimately, the goal needs to be an improvement in survival or an improved quality of life. C

DEBU TRIPATHY, M.D.
EDITOR-IN-CHIEF
Professor of Medicine
Chair, Department of Breast Medical Oncology
The University of Texas MD Anderson Cancer Center

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HIIT It!

A patient with prostate cancer under active surveillance may encounter the fear that their cancer might progress, causing stress and anxiety. However, HIIT workouts may help put them at ease. *By* COLLEEN MORETTI

PERFORMING HIGH-INTENSITY INTERVAL TRAINING (HIIT) has previously been shown to improve physical health and is now demonstrating improvement in psychological health for patients with prostate cancer who are under active surveillance, according to recent study results. For some patients with low-risk prostate cancer, active surveillance may be their treatment direction, meaning the care team is monitoring the cancer closely, allowing a patient to avoid immediate treatment and side effects.

However, study author Kerry S. Courneya explained this period may cause some men to experience psychological distress, affecting their quality of life. "It's a bit of a helpless feeling to have cancer, and nothing (is) really being done about it," Courneya, a professor and Canada Research Chair at the University of Alberta in the Faculty of Kinesiology, Sport, and Recreation, said in an interview with *CURE*®. Some of the anxiety may come from waiting around, feeling nervous that it could get worse and they might need treatment — what Courneya called a fear of cancer progression.

He and colleagues evaluated whether exercise, which has been shown to improve psychological health in patients with cancer, would help men with prostate cancer on active surveillance improve their mental health. They examined the effects HIIT had on a patient's phycological state, including cancer-specific anxiety, fear of cancer progression, quality of life and psychological outcomes. The trial included 52 patients with prostate cancer who were randomized to either a 12-week HIIT program (26 patients) or usual care (26 patients) during active surveillance.

Compared with usual care, HIIT significantly improved patients' cancer-specific anxiety, fear of cancer progression, hormonal symptoms, perceived stress, fatigue and self-esteem. Courneya noted these improvements enhance a patient's quality of life because they don't feel as stressed.

"If there's anything we can do from a stress management or anxiety-reduction perspective, that will improve (patients') quality of life," he said. "(It) will allow them to just cope with having that disease but still feel psychologically healthy." He also added that the anxiety and stress can be so overwhelming for these men, some of them will choose to undergo treatment anyway, which could increase their risk of side effects that may be harmful and still impact daily life. However, he hopes these results may deter from that option.

"Even though the disease itself doesn't really need treatment and the doctor says it's fine, at some point, some of these patients say, 'Look, I just want it removed. I want the surgery or the radiation therapy.' Just because of the psychological impact of the disease," he noted. "We think these findings may help men stay on active surveillance longer and hopefully avoid treatments all together."

Additional results from a previous trial Courneya conducted demonstrated that HIIT also improved physical health, including cardiorespiratory fitness, reduced prostate-specific antigen levels and, for some, slowed the biochemical progression of the disease. He added that practicing other physical activities, such as walking, can also be helpful in improving psychological impacts during prostate cancer. However, the HIIT programs focus on a higher intensity, so a patient may become stronger in a physiological aspect than they would otherwise, improving their stress response.

"That underlying physiological capacity can become a buffer against stress and anxiety," he concluded. "But it's (also) the sense of feeling like you're doing something for yourself. Twiddling your thumbs and waiting for the disease to progress is one thing, but (when you're exercising), you feel like (you're) actually doing something that may slow the progression of the disease, (which) can have a positive psychological impact."

How to HIIT It

COURNEYA SAID STARTING a high-intensity interval training (HIIT) program like this, depends on the patient's current physical condition. Whether they are already working out frequently will determine how much HIIT they can do at a time, but it is a working-up process.

Before starting a HIIT program, a patient should be in fairly good physical health. Courneya suggests starting with just walking for a few minutes a few times a week, building up to 30 minutes almost every day, then the intervals can be incorporated. He also added that when starting a HIIT program, it is important to do it at your own pace and build it up slowly.

The length of the HIIT intervals can vary from 20 to 30 seconds to four to five minutes. There is no magic duration or number of intervals. Courneya suggests starting with shorter high intensity intervals (30 seconds to one minute) and building up to longer high intensity intervals (two to four minutes). He also suggests starting with fewer intervals (two to three) and increasing up to eight intervals. The recovery intervals (usually lighter intensity) can be as long as needed for recovery before the next high-intensity interval.

One specific type of HIIT is sprint interval training. "We call it sprint interval training because it's all out for a short period of time," he said. "You can just play with it in terms of what feels good (and) what is working, but if you can incorporate a little bit of that burst of HIIT, even for 30 seconds, … it has a lot of health benefits."

HIIT Walking

Start in small sections each day, with a total of five minutes of training, then work your way up to 10 or even 15 minutes. Walk at a normal pace for two minutes, switch to a light jog for two minutes, then back to the normal walking pace for two minutes. Finally, switch back to the light jog for two more minutes.

HIIT Treadmill

Walking uphill can also be great for cardiovascular health, Courneya noted. Walk on the treadmill for two minutes at no incline, then increase the incline 5% to 10% for two minutes. Continue repeating for 10 to 15 minutes and build up your stamina more and more each day.

HIIT Elliptical

Start off with five minutes at your standard speed, then push to your full-out speed for one minute, and then back to five minutes of standard speed.

START WITH » Short high-intensity intervals (30 seconds to one minute)

BUILD UP TO » Longer high-intensity intervals (two to four minutes)

ROBERT HOLLANDER's passion for making wine became a personal purpose after he received a diagnosis of metastatic prostate cancer.

Winemaking for a Cause

After a metastatic prostate cancer diagnosis, Robert Hollander decided to bring together his love of wine and his journey with cancer to create a foundation to support the research field.

By COLLEEN MORETTI

HOLLANDER PROVIDED BY SUSAN HOLLANDER; WINE: EVERYTHING BAGEL / STOCK.ADOBE.COM

ROBERT HOLLANDER, 67, DISCOVERED his love of wine after working as a waiter/bartender through medical school and continued to show interest throughout residency. In 2007, he even started his own small-volume winery, 2Red Winery. However, his passion changed to purpose in 2009 when he received a diagnosis of metastatic prostate cancer.

His journey with cancer began in 2006, when he started getting his "adult medical tests." His prostate-specific antigen (PSA) test was slightly elevated at 4.5. A month later, it was tested again and was even higher. His doctor at the time referred him for 14 panel biopsies. The results of the biopsies showed no cancer, only an inflamed prostate. "Which is curious because there was no reason I should have had an inflamed prostate," Hollander said in an interview with *CURE*®. He was told he was "all good."

Anything over a 4 is often a "borderline range" of having prostate cancer and anything above that is over a 50% chance of diagnosis, according to the American Cancer Society. In 2008, after another PSA test, Hollander was at a 95. "When my PSA was 4.5, I wasn't that concerned. When it was 95, I was scared," he recalled.

He had another panel of 14 biopsies, which, once again, showed an inflamed prostate with no evidence of cancer. His urologist at a university told him, "Never check your PSA again. It's always going to be high."

A year after that, in 2009, during a rope climbing workout, he felt an odd and internal tug deep in his pelvis. After monitoring it for a week, he still felt it and decided to go to his primary care doctor, who ordered a CT scan, which found a "big bulky disease" in his pelvis. They found nodes as big as his fist and his PSA level was at 250. This confirmed his diagnosis of metastatic prostate cancer.

THE SETTLEMENT

"At that point, it was pretty clear to me (that) mistakes had been made along the journey," Hollander said. "The urologist who (told me to never check my PSA again because it's always going to be high) — there's a fine line between confidence and arrogance, and he was on the wrong side of that line."

After starting treatment for his disease, which consisted of androgen deprivation therapy (ADT), radiation and intermittent ADT, he decided to give the university's risk management department a call to let them know what had happened. He was going to send a lawsuit but wanted to give them a chance of settlement first. Because of bad medical advice and failure to diagnose his prostate cancer at a curable stage, the university offered him a settlement, which he took and later used to fund his newly created foundation.

A LOVE OF WINE AND A JOURNEY WITH CANCER

It was in 2007 that the Florida resident discovered he could create a small-volume winery based in Napa Valley, California. It started off great; the only problem was that one barrel of wine turned into 300 bottles, so he had a lot of leftover wine. But after receiving the settlement money he knew what to do.

"The time period was around the time of the cancer diagnosis, which was profoundly depressing," he said. "And (when I spoke) with the university's risk management department about a fair compensation — I was just trying to make sense of it all. I wanted to make something good of the whole thing."

The ideas of philanthropy, winemaking and the money from his settlement all came together, and he started the Robert and Susan Hollander Foundation to support further research for prostate cancer. "It put a positive note on the whole sorry situation," Hollander explained.

He said it feels great when he can give a monetary gift from the wine and foundation to a young researcher who is trying to make a change in the prostate cancer field and expand options for patients. "Everybody who goes through this journey has to find a way of dealing with a difficult situation," Hollander said. "The winemaking is fun, and having people enjoy it is great, too. It's a small thing, but (I'm) just trying to (make) the best out of a challenging situation."

DEALING WITH THE CARDS

After three years on ADT, Hollander decided to stop treatment because the side effects had become intolerable, and he has been off any type of therapy for 10 years. For now, he has a new campaign starting on Indiegogo to continue supporting prostate cancer research and his foundation.

He is excited to see how the campaign does and hopes to make more barrels and provide more support to researchers in the field. "There's a pessimistic, realistic side of me (that) stops me from being too optimistic," he said. "As for the future, tomorrow is promised to nobody, so it's just one day at a time."

For others going through a prostate cancer diagnosis, he advises them to not ask themselves why it happened to them, but instead try to make the most out of the cards they have been dealt.

As a physician himself, and spending most of his career in inpatient hospital medicine, he has realized that someone has it worse than him. During his own prostate cancer journey, he was caring for a younger man with an aggressive form of leukemia. When Hollander asked him how he stayed motivated, the young man said, "There's no alternative. You just have to look forward as best as you can, because there is no other realistic option."

"So that is the advice I would offer to others going through a cancer journey," Hollander said.

SOMEWHERE IN THE MIDDLE

PROSTATE CANCER IN THE OLIGOMETASTATIC SETTING — WHEN IT HAS NOT FULLY METASTASIZED — CAN NOW BE DETECTED AND TREATED EARLIER, IMPROVING SURVIVAL RATES.

By DON VAUGHAN

As a retired urologist, Mark Samberg, 72, of Sacramento, California, was familiar with what would happen after receiving a prostate cancer diagnosis in 2020. The advantage he had was better understanding his diagnosis, treatment and what came with it. The disadvantage was knowing what might happen to him.

"Being a physician, you know the right questions to ask," he says. "The bad part, of course, is that you've already seen the end of the book a few times, how the story could possibly end. That's the scary part."

One portion of his diagnosis he was familiar with was that his disease was in an oligometastatic setting — a sort of intermediate state that is more advanced than locally-confined disease but is not yet full-blown metastatic disease — a state that many patients may not know even exists. »

There is renewed interest in and growing clinical evidence of an "oligometastatic" state. Patients with oligometastases have a low volume of metastatic disease and limited sites of involvement and can experience prolonged disease-free intervals and possibly even improved overall survival through a combination of systemic and local therapies such as chemotherapy and radiation. An important aspect of this definition is that local therapies could feasibly be used to remove or eradicate areas of disease that are visible by scanning techniques and that medical therapy could address microscopic cancer that is not easily discernable.

DEFINING OLIGOMETASTATIC PROSTATE CANCER

The concept of an oligometastatic state was proposed in 1995 by oncologists Samuel Hellman and Ralph Weichselbaum, and prostate cancer, because of its long natural history and high prevalence, has become an important focus of research investigating the potential value of more precise treatment for oligometastatic disease.

"The oligometastatic hypothesis suggests that there may be patients who have disease spread to other parts of the body, but if we are very focused about treating them, we may be able to get all of the cancer or at least help the patient do better for longer and keep some of the medical approaches available for later," explains Dr. Ryan Phillips, a radiation oncologist at Mayo Clinic in Rochester, Minnesota.

"The reason to appreciate that it exists is we can better tailor the treatment to the individual."

According to Dr. Neha Vapiwala, professor and vice chair of education, radiation oncology, at the University of Pennsylvania in Philadelphia, oligometastatic prostate cancer has traditionally been defined by the detection of one to five metastatic sites on conventional imaging, such as CAT scans, PET scans, MRI and technetium bone scans.

» **MARK SAMBERG** is grateful he received PSMA PET imaging that detected his metastases. A standard work-up might have missed them, he says.

STACEY DOYLE

"In years past, using the conventional imaging technologies that were available, if we saw up to five lesions, the thinking was that this patient's disease might have a different natural history than someone who presents with many more lesions," Vapiwala notes. "We might be able to intervene with treatment that's more aggressive, targeting the handful of lesions that are seen, usually in addition to the normal systemic therapy we would give, with the idea of reducing tumor burden and, ideally, prolonging progression-free survival. But the 'quality' — meaning location and type — of metastatic disease also matters, not just the quantity. And this upper limit of five may not remain relevant as we learn more through molecular imaging."

Vapiwala says there are essentially two medical camps regarding the aggressive treatment of the prostate gland, if not yet treated, and/or sites of metastatic disease, and its role in enhancing survival. One side believes that while new imaging technologies detect small lesions earlier and more accurately, allowing for safer treatment, ultimately nothing changes regarding overall survival.

"Then you have individuals who say no, it's not just simply iatrogenic (relating to illness caused by medical examination or treatment) stage migration; we're not just diagnosing them earlier, but because we're intervening, we're making an impact," Vapiwala says. "And some of these aggressively treated patients do have a robust treatment response or at least remain on a protracted course, and do not inevitably develop explosive

STACEY DOYLE

disease later. This supports the idea that this is a different phenotype, a different biology altogether."

The most common metastatic sites for prostate cancer are lymph nodes and bones, and this was true for Samberg, who was found to have lesions on his lumbar spine and scapula, as well as some lymph nodes, following a diagnosis of prostate cancer.

Samberg's cancer journey started in 2019 when he began experiencing more frequent urination and other symptoms indicative of benign prostatic hypertrophy despite an active, healthy lifestyle. In early January 2020, he visited a colleague who told him his rectal exam was abnormal and referred him to a specialist at the University of California, San Francisco. By then, his prostate-specific antigen (PSA) level had progressed from 1.7 to 3.8 (the normal range is between 1.0 and 2.5).

Samberg underwent an MRI in February 2020, which he found concerning. A biopsy was scheduled, then everything shut down because of COVID-19. Months later, Samberg finally received his diagnosis and a Gleason score of 4+4, which is considered high-risk disease. Imaging during his pretreatment work-up revealed the metastases. Samberg's treatment included androgen deprivation therapy with leuprolide, stereotactic body radiation, radiation to the metastatic sites and several cycles of Keytruda (pembrolizumab) as part of a clinical trial.

Because of his work as a urologist himself, Samberg was familiar with the concept of an oligometastatic state. »

The term "oligometastatic" was not brought up during **CHUCK PAPPAS'** diagnosis, probably because he is a layman, he says.

However, this was not the case for Chuck Pappas, 72, of Plymouth, Minnesota, whose prostate cancer journey involved three separate incidences over a course of several years. A rise in his PSA heralded each new bout, suggesting metastases that were later confirmed via imaging. Pappas underwent prostate surgery, stereotactic body radiation and combined treatment with radiation and leuprolide. He was declared cancer free in May.

His care team at Mayo Clinic in Rochester, Minnesota, never used the phrase "oligometastatic disease," Pappas says, likely because he was a layman. "But I believe that's what I had because when they first started my radiation treatment, they found a few lesions, which later progressed to my lymph nodes," he observes. "Looking back, it certainly fits." Phillips confirmed that is what it was.

ADVANCES IN IMAGING

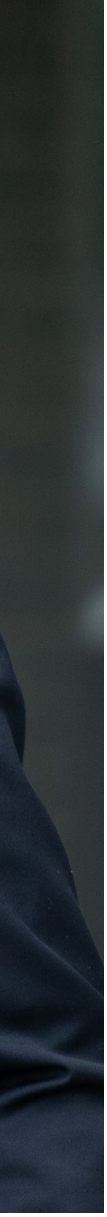
Oligometastatic disease is most effectively diagnosed through imaging, which is more sensitive today than ever before. One of the most effective new technologies is prostate-specific membrane antigen (PSMA) PET imaging, which has been available in Europe and Australia for several years and received U.S. Food and Drug Administration approval in 2021. This is the imaging technology that revealed Samberg's metastases.

"PSMA PET imaging has been a big game changer for us because it allows us to diagnose metastatic disease much earlier," says Dr. Peter Carroll, professor of urology at the University of California, San Francisco in the department of urology. "It has shown that when we do that, we change treatment recommendations substantially. In the past, we might have given radiation or hormonal therapy alone. Now, with earlier detection, we're offering treatments like stereotactic body radiation with or without hormonal therapy or surgery for metastatic disease. What we don't know yet is how that translates to long-term disease-free survival."

Samberg said he was grateful to receive PSMA PET imaging. "My metastases likely would not have been detected under our standard work-up regimen," he said. "In fact, they did the standard imaging and didn't see the lesions that the PSMA PET scan showed."

Equally exciting is the choline C-11 PET scan, which uses a radioactive form of the vitamin choline as a tracer to help detect sites of recurrent prostate cancer. This is the technology that revealed Pappas' nodal metastases. A low-dose CT scan is commonly done at the same time to help further show

LAUREN B PHOTOGRAPHY



> I believe the key for many is to turn prostate cancer from a lethal disease to a chronic disease. That's what we're trying to do.
>
> —DR. PETER CARROLL

internal anatomy, the Mayo Clinic reports.

Older imaging technologies, while not as sensitive, still have value, Vapiwala observes. "MRI can still be very useful, in particular, MRI of the pelvis," she notes. "There are also centers around the world that are very focused on whole body, or multiparametric MRI. In many places technetium scans remain standard for evaluation of the bony skeleton. But increasingly we're seeing PET imaging supplementing if not replacing these scans for staging and clinical decision-making."

The American Society of Clinical Oncology, in a report titled "Approach to Oligometastatic Prostate Cancer," advises a multimodal treatment approach to patients with oligometastatic disease "with evidence for surgery, radiotherapy, and systemic therapy, alone or in combination, improving patient outcomes."

Androgen deprivation therapy (ADT), in which the patient's testosterone level is lowered in an attempt to hold the cancer in check for as long as possible, has proved especially effective, notes Phillips. "There are other complementary medications, including more advanced androgen-directed therapies, that can make this approach last longer and be more effective," he adds. "What we're learning more and more is that for patients who have a limited number of detectable areas of spread, being more aggressive in treating those areas can add a lot of value and help patients live longer. The way we do that, most commonly, is with targeted radiation. There are also times where we use surgery or other ablation techniques such as radio frequency ablation or cryotherapy."

ANSWERING THE BIG QUESTIONS

Prostate cancer in the oligometastatic setting has been a topic of study for several years as researchers seek to better understand the disease and develop more effective diagnostic imaging technologies and treatment.

"There are some big questions around oligometastatic prostate cancer, and I believe we have the answers to many," says Carroll. "The first is, can we diagnose this disease state better than we had in the past? And the answer is yes. We're clearly seeing that when we diagnose it earlier, we're changing treatment recommendations based on historical paradigms in imaging. So we're diagnosing it more commonly and treating it differently. The big question is. Are the outcomes any better? How many quality-adjusted life years will it add? That remains to be determined. My feeling, based on the evidence to date, is that it will be beneficial. What I don't know is the magnitude of that benefit or the financial cost."

Vapiwala hopes to add to that discussion through the ongoing national phase III randomized INDICATE trial. Patients with rising PSA after prostatectomy and no evidence of metastases on conventional imaging all receive standard of care pelvic RT and short-term androgen deprivation but are randomly assigned based on their baseline PET scan finding to local therapy intensification with metastasis-directed RT if they have PET-positive disease outside the pelvis or system therapy intensification with apalutamide if they are PET-negative outside the pelvis.

"We're asking, if we find disease on PET only and make treatment decisions based on that, are we making a meaningful difference in clinical outcomes?" Vapiwala asks. "If we see a few lesions and chase after them, it might make us feel better, but are we actually helping the patient?"

Other areas of research opening doors include the following:

- "Outcomes of Observation vs Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer," published in 2020 in the *Journal of the American Medical Association*, found stereotactic ablative radiotherapy promising for men with recurrent hormone-sensitive oligometastatic prostate cancer who wish to delay the start of ADT.
- Researchers at the University of Florida are evaluating the outcomes of patients treated with an investigational radiation regimen using stereotactic radiotherapy for oligometastatic prostate cancer, and to establish efficacy and safety.
- Mayo Clinic is collaborating with Johns Hopkins University on research looking at oligometastatic prostate cancer treated with targeted radiation with or without the addition of a bone-specific radiopharmaceutical. "It's an infusion of radium, which goes to areas of bone disease and may treat microscopic spread in the bones that we can't yet detect," reports Phillips.

Thanks to recent advances in diagnosis and treatment, the risk that oligometastatic prostate cancer will eventually become terminal is far less than in years past, oncologists say. "All men who have metastatic disease are at risk of dying from it," notes Carroll. "I believe the key for many is to turn prostate cancer from a lethal disease to a chronic disease. That's what we're trying to do." C

TO TEST *or Not to* TEST

As PSA testing recommendations change and the debate surrounding testing continues, people with a high-risk of prostate cancer and their families need to stay informed.

By KATHERINE MALMO

John Salata says he is grateful his prostate-specific antigen (PSA) was tested when it was, even if it was by accident. When Salata was 48, his primary care doctor mistakenly checked the box for a PSA test when ordering his panel of bloodwork. When Salata's score came back high, she referred him to a urologist who gave him an antibiotic. A few months later, his PSA tested even higher. He had a biopsy and received a diagnosis of cancer. He had a radical prostatectomy (surgery to remove the prostate gland and seminal vesicles after a prostate cancer diagnosis) in January 2011.

"When the pathology came back, it was 60% cancerous and it had spread beyond the surgical margins," Salata recalls. "If we hadn't found it, then it probably would have spread outside the prostate within a few years. It would have spread throughout the body. Even at that point in time there are usually no symptoms, so there would've been no need for me to see a doctor. Because the guidelines didn't recommend testing until (age) 55 or 60, it would have gone unnoticed for some time. Then once you're at stage 4, the care is generally palliative." »

MGUIDO / STOCK.ADOBE.COM

JOHN SALATA says he feels grateful that his PSA was tested by accident and later led to a prostate cancer diagnosis.

> Because the guidelines didn't recommend testing until (age) 55 or 60, it would have gone unnoticed for some time.
>
> —JOHN SALATA

Changes in recommendations for PSA testing as a screen for prostate cancer are a frequent occurrence. Why is it so difficult to decide whether or when it should be done? And what do the changes mean for men over the age of 50 as they enter the risk zone for this cancer type?

WHAT IS PSA?

PSA is a protein made by prostate cells and released into the bloodstream. It is produced by both cancerous and noncancerous cells, but cancer cells tend to secrete PSA more directly into the blood, so PSA levels are often higher in patients with prostate cancer, according to Dr. Michael S. Leapman, associate professor of urology at Yale School of Medicine and clinical program leader of the Prostate and Urologic

ARIELLE GALLIONE

Cancers Program at Yale Cancer Center in New Haven, Connecticut. "The PSA test does not diagnose prostate cancer," Leapman says. "If you have a higher than average PSA, you're identified to be in a higher risk category that typically triggers further investigation."

PSA is specific to the prostate but not to prostate cancer, notes Dr. Mihir M. Desai, professor of clinical urology and director of robotic urologic surgery at Keck Medicine of USC in Los Angeles. High PSA levels also can be caused by infections, inflammation and other prostate procedures.

WHY DO RECOMMENDATIONS KEEP CHANGING?

As with many cancer types, some prostate cancers may be so slow growing that they will not affect a patient significantly in their lifetime, so their detection and treatment may end up being worse than the cancer having been left alone. To ensure that prostate cancer screening is focused on those who would benefit, there are multiple organizations that issue medical guidelines in the United States, including the American Urological Association, National Comprehensive Cancer Network and American Cancer Society. Each formulates its guidelines based on data from clinical trials that are available at that time. A patient may find that their PSA test is ordered by a primary care doctor who consults one source, and then by a urologist who consults another.

The U.S. Preventive Screening Task Force (USPSTF), an organization made up of public health and primary care experts, changed its PSA recommendations in 2018. According to their website, that year, the recommendation for men 55 to 69 years old to undergo periodic PSA-based screening for prostate cancer should be an individual one, and that clinicians should not screen men who do not express the preference. Additionally, the recommendations were against PSA-based screening in men 70 years and older.

"In 2012, the USPSTF issued a statement saying that no one should be screened for prostate cancer with the PSA test. At the time, the judgment from the USPSTF was that the net harms of screening outweighed the potential benefit," Leapman says.

This recommendation was based on the Prostate, Lung, Colorectal and Ovarian Cancer Screening (PLCO) trial. In the trial, investigators randomly assigned men into two groups: those who were given a PSA test and those who were not. The trial results, released in 2009, showed that the difference in number of deaths between the two groups was statistically insignificant.

Also in 2009, results of the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial were published. The trial was similar to the PLCO trial in that participants were randomly assigned into groups to receive PSA screening or not. However, results of the ERSPC showed a 29% relative reduction in mortality for the PSA-tested group. Why the difference?

"One question we asked was how was the U.S. study conducted?" Leapman adds. "The main concern was that there was significant contamination — about 90% of the people in the 'do not screen' group had actually received PSA testing at some point. It really minimized the potential benefit that could have been seen because men were getting diagnosed in both groups. That contamination was not as prevalent in the European study."

WHAT'S THE HARM OF TESTING?

"The test itself is just a blood test," Leapman says. "It's usually combined with other routine bloodwork. So it's not the test itself that is dangerous; it's really what happens downstream."

Often, the next step after receiving a high PSA test score is a biopsy. Dr. Kenneth Lin, professor of clinical family medicine at MedStar Georgetown University Hospital in Washington, D.C., says there can be real harm in this.

"Many men can be told they don't need a definitive intervention," Lin explains. "But nonetheless, when someone is walking around thinking there is some probability they have cancer, it often pushes them into treatments they don't need because they're never absolutely certain they don't have it. So a lot of men do have removal of the prostate or radiation therapy when they don't need to."

Henry Wigglesworth, 64, is one such patient. When he was 55, he started having his PSA level tested regularly, and it climbed slowly and steadily in the following years until it reached 5. A score between 4 and 10 is in the range of "suspicious," and approximately 25% of these patients with a score in that range have prostate cancer. Wigglesworth received a diagnosis of a nonaggressive form of prostate cancer in 2017.

"I still remember getting the call," Wigglesworth says. "My urologist said the results of my biopsy showed I had cancer. Nobody wants to hear that. Then he said the good news was that I had the least harmful type of cancer that exists. It was still very upsetting. I'm healthy in all other respects. I never thought I would have cancer."

That doctor recommended active surveillance that included frequent monitoring, but then told Wigglesworth that most men usually ended up opting for some form of treatment after five years or so. This prompted Wigglesworth to enroll in a study through the National Institutes of Health (NIH), where they monitored his cancer with regular PSA tests, MRIs and biopsies. They didn't find any signs of progression.

When Wigglesworth later went to a urologist about his enlarged prostate, he explained his history, and the urologist said he never would have ordered the biopsy because Wigglesworth's inflamed prostate likely had caused the high PSA result.

Approximately a year after the first biopsy, Wigglesworth returned to »

It has become a part of **WIGGLESWORTH**'s daily routine to jog alongside his son, who rides his unicycle to school.

BOB RIVES

NIH. His doctor found a lesion, and Wigglesworth had another biopsy. He left the NIH with a catheter that remained in for four days. When the results came back inconclusive, the doctor ordered another biopsy.

"And I said, 'No,'" Wigglesworth recalls. "I'm sorry. I'm not going to let you poke me again with that needle."

While Wigglesworth has opted for active surveillance for his prostate cancer, Salata's story shows the dangers of not testing. His cancer could have been diagnosed later in life, at the recommended age for testing, when, as he said, it could have been too late.

WHAT ARE THE CURRENT RECOMMENDATIONS?

After the results of the ERSPC trial in 2018, the USPSTF updated its recommendations to state doctors should discuss the benefits and risks of PSA screening with patients who are between the ages of 55 and 69.

"PSA testing shouldn't be a knee-jerk reaction," Desai explains. "If patients are warned upfront that 'Look, even if we do detect prostate cancer, it may be low risk and low grade, and we don't even need to treat it,' then they're much more accepting of that fact afterward, so you can minimize the risk of overtreatment."

Leapman says the use of active surveillance (close monitoring) as a form of treatment increased in the years USPSTF did not recommend PSA screening. This means prostate cancer is less likely to be overtreated. Desai uses a number of tools to assess a patient's prostate cancer risk, including looking at the trajectory of their PSA numbers.

"If somebody has a brisk upshoot that doesn't go down, then that's more concerning," Desai says. "If it happens in somebody who has a strong family history, that is concerning. African American men have a higher risk of prostate cancer, so the trigger for a biopsy is lower." The general trigger, or signal, to do a biopsy is when the PSA is at 4 or higher. However, if there is a quick upshoot, if the patient is Black or if there is a family history of prostate cancer, physicians may decide to do a biopsy with a lower PSA level.

But even with discussion, there are still overlooked costs of running PSA tests. "I'd rather spend five minutes counseling somebody about nutrition or exercise," Lin says. "But I may not have that time because I'm committed to discussing this test, which I think has a pretty marginal benefit at best."

WERE THERE FEWER PROSTATE CANCER TESTS BETWEEN 2012 AND 2018?

Leapman says the number of men given PSA tests decreased by approximately 15% between 2012 and 2018. "After 2018 when the guidelines were changed," he says, "there was a significant increase. We estimate that rates of testing have approximately gone back to levels prior to 2012."

There were fewer PSA tests given during those years, but was there a decrease in the number of prostate cancer cases diagnosed? "Overall the total incidence of prostate cancer has gone down because less testing means fewer biopsies, which means less detection," Desai says. "But there is also evidence that the incidence of advanced or metastatic disease has begun to go up."

Lin says the studies for these years can be challenging to interpret. "What I've seen is that the percentage of

HENRY WIGGLESWORTH kept up with regular PSA testing and later received a diagnosis of nonaggressive prostate cancer.

BOB RIVES

cancers being diagnosed at a more advanced stage has gone up relative to the lower, earlier-stage cancers," Lin says. "But you would expect that to happen because we were no longer screening as much. The proportions have changed. I haven't seen good data showing that the absolute number of late-stage cancers has gone up relative to the population."

WHAT DOES THE FUTURE HOLD?

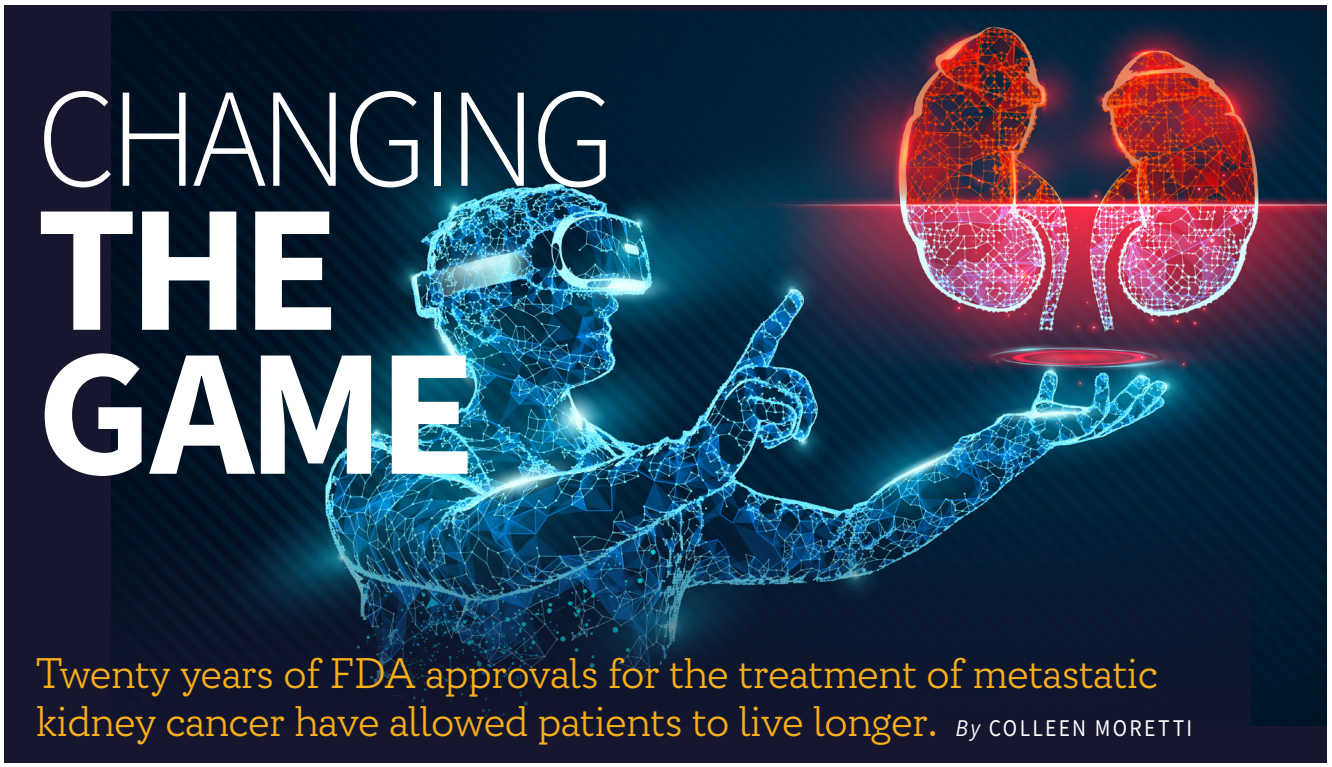
Although MRIs have been around for a while, Leapman says the quality of the image has improved and can reliably show cancer in the prostate. This makes the biopsy more targeted and accurate. "I think the MRI will hopefully spare some men biopsies," Lin says. "Or if they have to undergo a biopsy, it'll be more definitive."

There are also other blood and urine-based biomarkers that when taken together with a PSA, Leapman says, can help doctors calculate the patient's prostate cancer risk.

Salata and Wigglesworth say they have moved on with their lives. Salata says he was the first in his family to receive a diagnosis of prostate cancer, but his uncle and cousin also received diagnoses not much later. Salata's son, who is 26, is planning to have his first PSA test in the next few years.

Wigglesworth notes he recently talked to someone who received a diagnosis of late-stage prostate cancer due to an early PSA test. "And I thought, Oh my gosh, this test is amazing," he says. "Everybody should have it. But then there's the other side, the harm that can be done, not from the test itself, but from this odyssey that you have to go on to identify how it should be treated."

CHANGING THE GAME



Twenty years of FDA approvals for the treatment of metastatic kidney cancer have allowed patients to live longer. *By* COLLEEN MORETTI

TWENTY YEARS AGO, patients with metastatic kidney cancer were barely living beyond one year after diagnosis, and there were not many effective treatment options. But thanks to scientific advancements and an abundance of Food and Drug Administration (FDA) drug approvals, patients now are living longer.

Dr. Chung-Han Lee explained in an interview with *CURE*® that kidney cancer had long been thought of as a malignancy that was highly resistant to treatments such as chemotherapy and radiation. "I think that over the past 20 years we really have seen how the investments in scientific discovery have led to improved patient outcomes," said Lee, who is a medical oncologist at Memorial Sloan Kettering Cancer Center in New York City. "Kidney cancer, for the longest period of time, was a disease in which none of the systemic therapies worked. And then as soon as we truly understood the biology, we were able to rationally design treatments."

ADVANCEMENTS WITH APPROVALS

Dr. James Brugarolas, director of the kidney cancer program at Harold C. Simmons Comprehensive Cancer Center at UT Southwestern Medical Center in Dallas, noted that prior to 2005 there was only one drug approved by the FDA — limiting patients' options. "The past 20 years have been revolutionary for kidney cancer, perhaps more so than most other types of cancer," he said in an interview with *CURE*®. "But since 2005 there have been more than a dozen drugs approved for kidney cancer therapy."

The first metastatic kidney cancer treatments that demonstrated great progress were targeted therapies. They target proteins that control blood vessel growth and tumor nourishment.

Sutent (sunitinib) was approved in 2007 — Lee called this approval "pivotal." It was based on an 11-month progression-free survival (time during and after treatment when the patient lives without disease progression).

"I think (Sutent) was the first proof of concept demonstrating that this is a key molecular pathway that's important for kidney cancer," he said.

And then there was a stream of targeted therapies that received approval, including:

2009 Votrient (pazopanib) demonstrated a reduced risk of tumor progression or death by 54%, compared with placebo, and a progression-free survival of 9.2 months.

2012 Inlyta (axitinib) showed a 43% improvement in median progression-free survival compared with Nexavar (sorafenib), which was standard of care at the time.

2016 Cabometyx (cabozantinib) was approved for the treatment of patients with advanced kidney cancer who received prior lines of therapy. It was approved again in 2017 for first-line treatment.

2016 Lenvima (lenvatinib) in combination with Afinitor (everolimus) demonstrated a 14.6-month progression-free survival and 63% reduction in risk of disease progression or death compared with Afintior alone.

2021 Fotivda (tivozanib) demonstrated a progression-free survival of 5.6 months and objective response rate (the rate of a measurable response to the treatment) of 18%.

The past seven years brought the development of immunotherapy, Brugarolas said. These drugs boost a patient's immune system to recognize and destroy cancer cells more effectively. They include immune checkpoint inhibitors, PD-1 inhibitors, PD-L1 inhibitors and CTLA-4 inhibitors.

Drugs that have been approved over the past few years for metastatic kidney cancer include Opdivo (nivolumab), Yervoy (ipilimumab), Keytruda (pembrolizumab) and Bavencio (avelumab), as well as combinations of these. Brugarolas noted that the combination approvals have been groundbreaking in the field. The approval of Opdivo plus Yervoy has resulted in 50% survival rates at four years, he said.

"This has significantly changed how we treat patients with metastatic kidney cancer today," Brugarolas explained. "The past 20 years have revolutionized the care and prognosis of patients with kidney cancer."

IMPROVING QUANTITY AND QUALITY OF LIFE

"The survival rates have changed profoundly," Brugarolas said. Prior to the development of these therapies, patients with metastatic kidney cancer had five-year survival rates of only 10%.

But now, there are five-year survival rates of over 40%, and some combinations are resulting in response rates as high as 70%. "Response rates are particularly high for combinations of immunotherapies with targeted therapies," he added.

A few years ago, the median time on a first-line tyrosine kinase inhibitor, a type of targeted therapy, was nine to 12 months, and a long-term response on these therapies was 18 months. Now, with more recent combination therapies, the median response may extend to beyond 24 months, Lee added.

"We're now taking the median and shifting it even beyond to what we used to think long-time responses would be," he explained.

And with that comes a durability of response, which is progression-free survival that has exceeded three times that of the whole population. Years ago, it was uncommon for that to even be observed, but now with certain combinations, such as Opdivo plus Yervoy, one-third of patients are achieving a long durability of response.

"We're starting to entertain the idea that these people may actually be cured of their disease; however, certainly longer follow-up is necessary to establish that as the case," Lee said.

And so, over the past 20 years it is clear survival has improved for patients with metastatic kidney cancer. But what about the life they are living while receiving these treatments?

Lee noted that quality of life has not been negatively affected by any of these advancements. Although immunotherapy and targeted therapy have side effects, they are manageable, said Brugarolas.

Twenty years ago, patients were being treated with cytokines such as interferon and interleukin-2. The patients often felt like they had the flu, and many couldn't continue taking therapy. Some also experienced cytokine release syndrome to an extreme that they had to be treated in a hospital's intensive care unit.

But today, these treatments and their side effects are much more manageable in an outpatient setting. For example, with immune checkpoint inhibitors, some patients may develop autoimmune side effects, but those who do not can have a quality of life that is minimally affected by these drugs. "I think that from an efficacy standpoint, a quality-of-life standpoint and a durability standpoint, we've seen significant progress," Lee said.

TACKLING THE NEXT 20 YEARS

Both Lee and Brugarolas agreed that there is more work to be done, and that is what the *next* 20 years are for. "I think that even though we have made a lot of progress in the past 20 years, until we get to the point where we're curing all of our patients, I think there is still a tremendous amount of progress to be done," Lee said.

Brugarolas agreed. "One challenge — and our dream — is to be able to cure all patients with metastatic kidney cancer," he said.

He added another challenge will be in precision medicine, which tailors the drug to a particular patient and their genetic makeup. Lee also highlighted this and discussed a drug he is excited about, Welireg (belzutifan), which was developed based on seminal discoveries at UT Southwestern and targets a transcription factor at the root of the cancer.

They also both agreed that the treatment of non-clear cell kidney cancer will need more focus in the next 20 years. Approximately 70% of patients with kidney cancer have clear cell kidney cancer, so that is what most of the treatments are indicated for. However, this leaves the rest — patients with non-clear cell kidney cancer — with an unmet need for more treatment options.

"There are a few challenges that we have to tackle over the course of the next 20 years," Brugarolas concluded. "This is just the beginning."

The kidney cancer field used to be "depressing," Lee explained, as a lot of work went into developing treatments but not much panned out. But over the past 20 years there has been great success, which ultimately has benefited patients.

"It's really blossomed as we've seen success," he concluded. "This has truly translated to benefits for the patients. When we talk about these improvements and the number of years a patient has, that's extra vacations, time with family, family reunions, anniversaries. I think it really does translate to very tangible outcomes." C

Another Tool in the Toolbox for Prostate Cancer

FANS for the CURE

PSMA PET imaging has emerged as a treatment option for prostate cancer, and patients need to discuss with their physician whether it's right for them. *By* KRISTIE L. KAHL

DR. DANIEL P. PETRYLAK

IN RECENT YEARS, A new a type of imaging — and potential treatment option — has surfaced with a nod from the Food and Drug Administration (FDA) for men with prostate cancer. The indication is for those at risk of metastatic disease and those previously treated who have developed biochemical recurrence as shown by rising prostate-specific antigen (PSA) levels.

Prostate-specific membrane antigen, or PSMA, has yielded exciting results, offering a "new tool in the toolbox," for patients, according to Dr. Daniel P. Petrylak, a professor of medicine (medical oncology) and urology, as well as chief of genitourinary oncology and co-leader of Cancer Signaling Networks at Yale Cancer Center in New Haven, Connecticut.

In *CURE*®'s "Speaking Out" video series, Petrylak discussed what PSMA is and what is on the horizon with the imaging agent.

Q: Can you explain the use of PSMA and what it is?

A: PSMA has been around since about 1990. It is a membrane protein that sits on the surface of the prostate cancer cell. It actually is a folate transporter, strangely. It was originally looked at in terms of trying to develop a blood test similar to PSA. PSA has its own advantages and disadvantages, but it really is not shed into the bloodstream. PSMA is distinct from PSA, I think it's important to note. PSMA is expressed in practically all prostate cancer cells, probably 90%. It's also expressed on the vasculature of other tumors. But interestingly, it's not in the blood vessels of prostate cancer. So it's a bit of a paradox. And people can't explain that observation.

There have been a variety of ways of trying to image prostate cancer using PSMA, and it's really been evolving over the past 20 years or so. There was a previously (FDA-approved agent) … that used an antibody that recognized an internal epitope of the PSMA molecule. It was not as accurate because it didn't catch what was on the outside of the cell. And it wasn't as easily admissible; it picked up dead cells in that situation. But nonetheless, it was FDA approved. And there were some drawbacks to it: a lot of false-positive (results). There are newer next-generation PSMA imaging techniques being used. These involve PSMA gallium, other ligands that recognize PSA aside from monoclonal antibodies, and these are more sensitive in picking up prostate cancer than, for example, standard CT imaging or bone scans.

Q: Where are we with the use of PSMA?

A: Right now, we have several different PSMA tests, imaging agents, that are approved for detecting prostate cancer. And these are predominantly being used for detecting occult disease. If we have a patient

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who comes in with a negative CT scan or bone scan, but a rising PSA, we potentially can identify sites of disease that may not be picked up on the scans for treatment of oligometastases or determine whether the disease is truly localized. Additionally, it's being used as an imaging agent to select patients to be treated with isotopes, particularly PSA lutetium. And those patients who image positively are more likely to respond to this particular antibody or these isotopes.

Q: Can you discuss some of the trials we should keep our eye on?

A: The VISION trial evaluated PSMA lutetium in patients who had (improved) or had progressed after a taxane-(based chemotherapy) and next-generation anti-androgen (therapy), and this was compared with best supportive care. That showed a survival benefit in favor of PSMA lutetium. There was another trial to compare PSMA lutetium, a randomized phase 2 (trial) that showed that in comparison with cabazitaxel, this had a better progression-free survival (the time from treatment to disease progression or worsening), but there's no overall survival (the time from treatment that a patient is alive) difference. Those are the two trials I think are important that have come out recently.

There are studies that are now moving these agents up earlier. There's one trial looking at this in hormone-sensitive disease, giving PSMA lutetium along with hormone therapy and then seeing whether this will improve survival as well. There's been a trend, as with all our agents such as chemotherapy and next generation anti-androgens, to move these upfront into the treatment of diseases.

Q: What do we have to look forward to with PSMA in prostate cancer?

A: Right now, I think it's a another tool in our toolbox. It does improve overall survival. It does improve progression-free survival, but it is not a cure. And I think that's very, very important for patients to remember. It's another treatment regimen that we can use. It does offer a different target than immunotherapy, chemotherapy or hormones or, for that matter, targeted therapy with agents such as Lynparza (olaparib) and Rubraca (rucaparib). You have to discuss with your doctor about when's the right time to administer this in relationship to the other treatments. C

Transcription edited for clarity and conciseness.

Something Old, *Something New*

BCAN
Bladder Cancer Advocacy Network

A vast array of new drugs are avaliable to treat bladder cancer, but researchers are also studying new ways to use the older agents. *By* KRISTIE L. KAHL

ALTHOUGH THERE ARE MANY Food and Drug Administration-approved drugs to treat patients with advanced urothelial carcinoma, researchers continue to work to increase survival by evaluating new agents. However, they aren't entirely reinventing the wheel.

As part of the *CURE*® "Speaking Out" video series, Dr. Tracy L. Rose, an assistant professor of medicine in the Division of Oncology, Department of Medicine, at UNC Health in Chapel Hill, North Carolina, discussed the need for more treatment options in this space and how currently available agents are being investigated in combination with one another.

Q: Can you explain relapse in urothelial carcinoma following standard of care in the first-line setting?

A: Some of this answer depends on the stage of the cancer that you're talking about. (For) advanced cancer that is still localized, what we call muscle-invasive bladder cancer, or even lymph node-positive bladder cancer, when patients get surgery or radiation, typically we do cure some of those patients. In other patients, their cancer comes back after that aggressive treatment. And we call that relapse.

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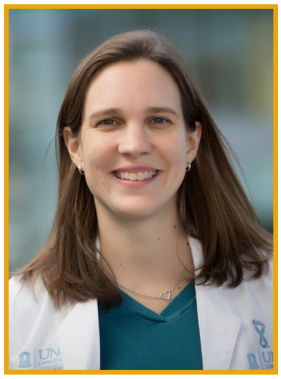

DR. TRACY L. ROSE

Setting Our Sights On Living Longer

PADCEV® was studied in adults with advanced bladder cancer who had previously received an immunotherapy and platinum-containing chemotherapy. In the study, median overall survival with PADCEV was 13 months versus 9 months with chemotherapy.

Please see Important Safety Information below and talk to your doctor about side effects.

IMPORTANT SAFETY INFORMATION

What is the most important information I should know about PADCEV?

PADCEV may cause serious side effects, including:

Skin reactions. Severe skin reactions have happened in people treated with PADCEV; in some cases severe skin reactions have caused death. Most severe skin reactions occurred during the first cycle (28 days) of treatment but may happen later. Your healthcare provider will monitor you during treatment and may prescribe medicines if you get skin reactions. Tell your healthcare provider right away if you develop any of these signs of a new or worsening skin reaction:

- target lesions (skin reactions that look like rings)
- rash or itching that continues to get worse
- blistering or peeling of the skin
- painful sores or ulcers in mouth or nose, throat, or genital area
- fever or flu-like symptoms
- swollen lymph nodes

See **"What are the possible side effects of PADCEV?"** for more information about side effects.

WHAT IS PADCEV?

PADCEV is a prescription medicine used to treat adults with bladder cancer and cancers of the urinary tract (renal pelvis, ureter or urethra) that has spread or cannot be removed by surgery. PADCEV may be used if you:

- have received an immunotherapy medicine **and** chemotherapy that contains platinum, **or**
- you are not able to receive a chemotherapy that contains the medicine cisplatin and you have received one or more prior therapy.

It is not known if PADCEV is safe and effective in children.

Before receiving PADCEV, tell your healthcare provider about all of your medical conditions, including if you:

- are currently experiencing numbness or tingling in your hands or feet
- have a history of high blood sugar or diabetes
- have liver problems
- are pregnant or plan to become pregnant. PADCEV can harm your unborn baby. Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with PADCEV
- are breastfeeding or plan to breastfeed. It is not known if PADCEV passes into your breast milk. Do not breastfeed during treatment and for at least 3 weeks after the last dose of PADCEV

Females who are able to become pregnant:

- Your healthcare provider should do a pregnancy test before you start treatment with PADCEV.
- You should use an effective method of birth control during your treatment and for at least 2 months after the last dose of PADCEV.

Males with a female sexual partner who is able to become pregnant:

- If your female partner is pregnant, PADCEV can harm the unborn baby.
- You should use an effective method of birth control during your treatment and for at least 4 months after the last dose of PADCEV.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Taking PADCEV with certain other medicines may cause side effects.

How will I receive PADCEV?

- PADCEV will be given to you by intravenous (IV) infusion into your vein over 30 minutes.
- You will receive your PADCEV over periods of time called cycles.
  - Each PADCEV cycle is 28 days.
  - You will receive PADCEV on days 1, 8 and 15 of every cycle.
- Your healthcare provider will decide how many treatment cycles you need.
- Your healthcare provider may do blood tests regularly during treatment with PADCEV.

What are the possible side effects of PADCEV?

PADCEV may cause serious side effects, including:

- **Skin Reactions.** See **"Skin Reactions"** above for more information.

PADCEV is approved to treat your **advanced bladder cancer*** if you have received:

Immunotherapy and platinum-containing chemotherapy

OR

Prior therapy and could not receive cisplatin chemotherapy

Ask your healthcare professional if PADCEV is right for you or your loved one

Visit **PADCEV.com** or call **1-888-4PADCEV (1-888-472-3238)** for more information

*Bladder cancer and cancers of the urinary tract (renal pelvis, ureter or urethra) that has spread or cannot be removed by surgery.

- **High Blood Sugar (hyperglycemia).** You can develop high blood sugar during treatment with PADCEV. High blood sugar, a serious condition called diabetic ketoacidosis (DKA), and death have happened in people with and without diabetes who were treated with PADCEV. Tell your healthcare provider right away if you have any symptoms of high blood sugar, including: frequent urination, increased thirst, blurred vision, confusion, it becomes harder to control your blood sugar, drowsiness, loss of appetite, fruity smell on your breath, nausea, vomiting, or stomach pain.
- **Lung problems.** PADCEV may cause severe or life-threatening inflammation of the lungs that can lead to death. Tell your healthcare provider right away if you get new or worsening symptoms, including trouble breathing, shortness of breath, or cough.
- **Peripheral neuropathy.** You may develop nerve problems called peripheral neuropathy during treatment with PADCEV. Tell your healthcare provider right away if you get new or worsening numbness or tingling in your hands or feet, or muscle weakness.
- **Eye problems.** You can develop certain eye problems during treatment with PADCEV. Tell your healthcare provider right away if you have dry eyes, blurred vision, or any vision changes. You may use artificial tear substitutes to help prevent or treat dry eyes.
- **Leakage of PADCEV out of your vein into the tissues around your infusion site (extravasation).** If PADCEV leaks from the injection site or the vein into the nearby skin and tissues, it could cause an infusion site reaction. These reactions can happen right after you receive an infusion, but sometimes may happen days after your infusion. Tell your healthcare provider or get medical help right away if you notice any redness, swelling, itching, or discomfort at the infusion site.

The most common side effects of PADCEV include:

- skin rash
- changes in liver and kidney function tests
- increased sugar (glucose) in the blood
- tiredness
- numbness or tingling in your hands or feet, or muscle weakness
- decreased white blood cell, red blood cell, and platelet counts
- hair loss
- decreased appetite
- diarrhea
- decreased sodium, phosphate and protein (albumin) in the blood
- nausea
- itching
- change in sense of taste
- increased uric acid in the blood
- increased lipase (a blood test done to check your pancreas)
- decreased weight
- dry skin

If you have certain side effects, your healthcare provider may decrease your dose or stop your treatment with PADCEV for a period of time (temporarily) or completely.

PADCEV may cause fertility problems in males, which may affect the ability to father children. Talk to your healthcare provider if you have concerns about fertility.

These are not all the possible side effects of PADCEV.

Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see Brief Summary of full Prescribing Information (Prescription Drug Facts), with an Important Warning of Serious Side Effects on adjacent page.

astellas Seagen

PADCEV®
enfortumab vedotin-ejfv
Injection for IV infusion 20 mg & 30 mg vials

Prescription Drug Facts

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Purpose

PADCEV (enfortumab vedotin-ejfv) injection for IV infusion 20mg or 30mg vials..... .Cancer Treatment

Important Warning Severe skin reactions have happened in people treated with PADCEV, in some cases severe skin reactions have caused death. Most severe skin reactions occurred during the first cycle (28 days) of treatment but may happen later. Your healthcare provider will monitor you during treatment and may prescribe medicines if you get skin reactions. Tell your healthcare provider right away if you develop any of these signs of a new or worsening skin reaction: ■ target lesions (skin reactions that look like rings) ■ rash or itching that continues to get worse ■ blistering or peeling of the skin ■ painful sores or ulcers in mouth or nose, throat, or genital area ■ fever or flu-like symptoms ■ swollen lymph nodes
See ***"Warnings"*** below for more information about serious side effects of PADCEV.

Uses Treatment of adults with bladder cancer and cancers of the urinary tract (renal pelvis, ureter, or urethra) that has spread or cannot be removed by surgery. PADCEV may be used if you:
■ have received an immunotherapy medicine **and** chemotherapy that contains platinum, **or**
■ you are not able to receive a chemotherapy that contains the medicine cisplatin and you have received one or more prior therapy.
It is not known if PADCEV is safe and effective in children.

Warnings

Ask a doctor before use if you have

■ numbness or tingling in your hands/feet ■ have a history of high blood sugar or diabetes ■ have liver problems

What are the possible serious side effects of PADCEV?

■ skin reactions. See ***"Important Warning"*** above ■ high blood sugar (hyperglycemia), including diabetic ketoacidosis (DKA), sometimes resulting in death ■ lung problems ■ nerve problems (peripheral neuropathy) like tingling in your hands or feet or muscle weakness ■ eye problems ■ infusion site reactions if PADCEV leaks out of your veins into tissues around your infusion site (extravasation)

Tell your doctor if you have

■ target lesions (skin reactions that look like rings), rash/itching that continues to get worse, skin blistering or peeling, painful sores in the mouth, nose, throat, or genital area, fever/flu-like symptoms, or swollen lymph nodes ■ frequent urination, increased thirst, blurred vision, confusion, it becomes harder to control your blood sugar, drowsiness, loss of appetite, fruity smell on your breath, nausea, vomiting, or stomach pain ■ trouble breathing, shortness of breath, or cough ■ numbness or tingling in your hands or feet or muscle weakness ■ dry eyes, blurred vision, or any vision changes ■ redness, swelling, itching, or discomfort at the infusion site, or get medical help right away.

If pregnant, able to become pregnant, or have a partner who is able to become pregnant

■ PADCEV can harm your unborn baby, talk to your doctor ■ females should use effective birth control during treatment and for at least 2 months after the last dose of PADCEV ■ males should use effective birth control during treatment and for at least 4 months after the last dose of PADCEV

If breastfeeding

■ do not breastfeed during treatment and for at least 3 weeks after the last dose of PADCEV

Fertility

■ PADCEV may cause fertility problems in males, which may affect the ability to father children

PADCEV®
enfortumab vedotin-ejfv
Injection for IV infusion 20 mg & 30 mg vials

081-0571-PM 07/21

Prescription Drug Facts Continued

Most Common Side Effects

■ Skin rash ■ changes in liver and kidney function tests ■ increased sugar (glucose) in the blood ■ tiredness ■ numbness or tingling in your hands or feet, or muscle weakness ■ decreased white blood cell, red blood cell, and platelet counts ■ hair loss ■ decreased appetite ■ diarrhea ■ decreased sodium, phosphate, and protein (albumin) in the blood ■ nausea ■ itching ■ change in sense of taste ■ increased uric acid in the blood ■ increased lipase (a blood test done to check your pancreas) ■ decreased weight ■ dry skin

If you have certain side effects, your healthcare provider may decrease your dose or stop your treatment with PADCEV for a period of time (temporarily) or completely.

These are not all of the possible side effects of PADCEV. **You may report side effects to FDA at 1-800-FDA-1088** or **www.fda.gov/medwatch**.

Directions

■ PADCEV will be given by intravenous (IV) infusion over 30 minutes ■ you will receive PADCEV over periods of time called cycles ■ each cycle is 28 days and PADCEV will be given on days 1, 8, and 15 of every cycle ■ your doctor will decide how many treatment cycles you need ■ your doctor may do blood tests regularly during your treatment

Other Information Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Taking PADCEV with certain other medicines may cause side effects.

If you would like more information about PADCEV, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about PADCEV that is written for healthcare professionals (full Prescribing Information) which includes more information about the ***Important Warning*** with PADCEV.

Inactive Ingredients histidine, histidine hydrochloride monohydrate, polysorbate 20, and trehalose dehydrate.

PADCEV®
enfortumab vedotin-ejfv
Injection for IV infusion 20 mg & 30 mg vials

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That is different from the patient with metastatic or stage 4 cancer, the advanced urothelial cancers. For many of those patients, we can get their cancer to shrink with first-line treatment, which typically is chemotherapy. But for the majority of patients with stage 4 disease, at some point their cancer starts to grow again. And standardly, we give chemotherapy and then we immediately give immunotherapy or immune therapy in a setting that we call maintenance to try to prolong the time until that cancer comes back. But for most patients with stage 4 metastatic urothelial cancer after chemotherapy and even immunotherapy, at some point, their cancer will grow again. It's really a conversation from the beginning about this care continuum, about how aggressive we want treatment to be. What (are the) priorities, and how (do we) handle that?

Q: Why is there a need for more treatment options in this space?

A: The great news in bladder cancer is that it's getting better and better. The number of treatment options has really exploded in the past few years in a way that we hadn't seen for decades. … We have so many more options. Despite these, for the majority of patients with advanced or metastatic bladder cancer, their cancer figures out how to grow despite all these treatments and, eventually, for most patients, that cancer takes their lives. Clearly, we can still do better. And there's a ton of work being done to advance the field. But we haven't yet found that miracle cure for the majority of patients with advanced or stage 4 cancers. So that's what we're trying to do.

Q: Can you talk about what antibody-drug conjugates are and how they work in bladder cancer?

A: This is a newer class of drugs being used in a number of different cancers, but (they) have had relatively good success in bladder cancer. Classically, we gave standard chemotherapy, which went throughout the whole body and disrupted fast-growing cells' ability to grow. (Chemotherapy) specifically treats cancer cells, because they tend to be fast growing, but (this type of treatment has) a lot of side effects. … Now we've developed, essentially, targeted chemotherapy.

What we do is take an antibody, which is a molecule that can be targeted to bind to a protein in the body, and then we attach chemotherapy to it. And so you can target the chemotherapy more specifically to certain things.

For example, there is a drug called Padcev (enfortumab vedotin) that's approved for metastatic or advanced bladder cancer, and it is an antibody to a protein called Nectin-4, which is expressed on the majority of bladder cancers. And (the antibody is) attached to a piece of chemotherapy. Now we take the chemotherapy and we direct it to any cells that have Nectin-4 on them, which include bladder cancer cells. So you're not delivering the chemotherapy to parts of your body that you don't want to give chemotherapy to. It's still not perfect, because there are also other cells, such as skin cells, that have these proteins on it. You do get some side effects, but it's essentially more targeted chemotherapy because it's bound to an antibody.

Q: Are there any drugs or combinations in the advanced or metastatic setting that are on the horizon?

A: There are a number of drugs that are approved in the advanced urothelial cancer setting. We've had chemotherapy for a long time. And more recently, a number of immunotherapy options either in the maintenance or what we call the relapsed setting (were introduced). And now there are a couple of other more targeted drugs. There are the antibody-drug conjugates enfortumab vedotin and Trodelvy (sacituzumab govitecan). And then there's another targeted therapy called Balversa (erdafitinib), which targets patients with mutations in FGFR, one of the proteins commonly mutated in bladder cancer.

And then, there are lots of really exciting clinical trials going on in a lot of different spaces. For example, we're testing a combination of enfortumab vedotin and immunotherapy, which has some pretty good preliminary data to see whether that's better than chemotherapy in the first line. We're looking at those same drugs in earlier-stage muscle-invasive bladder cancer, both before surgery and potentially after surgery. Similarly, researchers are looking at erdafitinib, which is the FGFR inhibitor, in earlier settings. And (researchers also are looking) at different types of immunotherapy to stimulate patients' immune systems by unblocking other pathways and at other antibody-drug conjugates. I mentioned Nectin-4, but there are also antibody-drug conjugates against (a protein) called HER2.

There's a vast array of new drugs, but (researchers also are studying) new ways to use drugs that we already have. It goes back to the conversation about clinical trials, which is the real way to test these and see whether we can improve standard of care. And we always encourage patients to consider clinical trials when they're making treatment decisions.

Transcription edited for clarity and conciseness.

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