Ruth Adewuya, MD (host):

Hello. You are listening to Stanford Medcast, Stanford CME's podcast where we bring you insights from the world's leading physicians and scientists. If you're new here, consider subscribing to listen to more free episodes coming your way. I am your host, Dr. Ruth Adewuya. This episode is part of the Stanford CME Prostate Cancer Series. The goal of the series is to enhance understanding of the increasingly complex treatment options, the latest diagnostics, and so much more. In addition to this podcast episode, our next activity is a live webinar taking place on March 21 at 9:00 AM Pacific Time. Learn more at prostatecancer.stanford.edu.

Ruth Adewuya, MD (host):

In today's episode, I will be chatting with Dr. James Brooks, and he will answer questions on the important features of prostate cancer, indications for PSA testing, and causes for elevated PSA. Dr. James Brooks is the Keith and Jan Hurlbut professor in the Department of Urology at Stanford University School of Medicine. Dr. Brooks joined the Stanford faculty in 1997, splitting his time between the laboratory and clinic, where he sees patients with prostate cancer. He's also the chief of urologic oncology in the Department of Urology, and he has been on the editorial board of The Prostate since 2000, and on the board of several other journals. Dr. Brooks, thank you so much for chatting with me today on prostate cancer.

James D. Brooks, MD (guest speaker):

It's my pleasure to be here.

Ruth Adewuya, MD (host):

Really great place to start in the conversation is to talk about PSA testing, or prostate-specific antigen testing. We hear PSA all the time. What is it? How accurate is it? And are there any risks and benefits to it?

James D. Brooks, MD (guest speaker):

Yeah. So PSA testing has been around really since the 1980s. It's been used extensively. This is a screening tool to look for cancer in men. Prostate is common enough that it makes sense. So you don't screen for rare cancers just because you need a tool or a test that has super high prediction ability, accuracy, if you will, whereas prostate cancer is terribly common. It's the most common cancer diagnosed at men, second leading cause of male cancer death. And as such, since it is so common, it's important to screen for it. PSA, as you'd mentioned, stands for prostate-specific antigen. It's a protein made only by the prostate. Every man has some PSA floating around in their bloodstream that can be measured. And in general in the US, we use a cutoff of four nanograms per ML, or four is the convenient number to remember, in Europe they use three, as an abnormal test.

Ruth Adewuya, MD (host):

When you say an abnormal test, what do you mean by that?

James D. Brooks, MD (guest speaker):

An abnormal test means that there is a risk that patient harbors prostate cancer. That risk is about 25% for a patient who has a PSA above four. If the PSA goes higher, the risk goes higher. So think about it like blood pressure. As the blood pressure gets higher, the risk of having serious cardiac disease goes higher.

In any event, we use this test as a screening tool for prostate cancer. We used to do PSA testing once a year. The latest guidelines are to do it less frequency in a man who is of average risk for prostate cancer.

Ruth Adewuya, MD (host):

You indicated that males have PSA floating around in their system. So what then is the indication to get PSA testing?

James D. Brooks, MD (guest speaker):

Like all of our screening tools, colonoscopy, mammography for breast cancer... Smokers, it's recommended that you do screening for lung cancer with low-dose CT scan. Screening for cancers can reduce the risk of dying of cancers. But the very simple reason is that when we're screening with PSA, we're looking to find cancers when they're still localized to the prostate, because then we can treat them. We can either remove the prostate or use radiation therapy to this destroy the cancers, and thereby prolong men's life expectancy.

Ruth Adewuya, MD (host):

If it is the most common cause of cancer in men, it's the second leading cause of death in men. Yet earlier on, you had indicated that the screening guidelines had changed from screening once a year to less than that. If it's that common, if it's that severe, can we unpack that? It seems like it should be more screening than less.

James D. Brooks, MD (guest speaker):

Yeah, that is a great question. What you allude to is a lot of the controversy that's been around PSA testing and the effectiveness of PSA testing. If you have an elevated PSA, a PSA above four, you have about a 25% chance that when we do a biopsy, we find cancer. That means that 75% of men have an elevated PSA for other reasons. However, we got into trouble with PSA testing. So when I started in this business as a urologist, which was the late 1980s, we were just starting to screen with PSA. And one of the things that happened is the number of cases of prostate cancer that were discovered as a result of screening absolutely went through the roof, and people freaked out. They panicked. And the reason they did is there has been data around since the 1940s that shows that men who die of other causes can fairly commonly have cancer in their prostate that didn't kill them.

James D. Brooks, MD (guest speaker):

They died with it rather than from it. And so once we started screening avidly with PSA testing, people were concerned that we were finding all of these autopsy-type cancers, that is, cancers that weren't destined to kill men. And what happened in fact after that is that we initially saw a big spike in prostate cancer diagnosis, and then it went down more or less onto the same rates we were seeing before we started PSA testing. The only thing that really changed significantly during that time was PSA testing. Enter a randomized trial, two randomized trials actually, that were done, one in Europe, one in the United States. The European screening trial, they call it ERSPC, enrolled 160,000 men, and it was a randomized trial, and they then followed men thereafter. And the screening done in that trial was PSA testing in most places every two years, every other year. In that study, by 10 years, they saw a relative of reduction in prostate cancer death rates of 20%.

James D. Brooks, MD (guest speaker):

Now, remember what I said here, which is relative drop in death rate. A man, in his lifetime in the United States, a Caucasian male has about a 3% chance of dying of prostate cancer. The place where this study done, in Scandinavia, men have about a 3.6% chance of dying of prostate cancer. That is, when they reach the finish line, the cause of death is prostate cancer. The men who were screened, it went down to 3%. So in the absolute sense, it's a pretty small drop in mortality, 0.6%. However, if you are one of those guys who had localized prostate cancer, that's a pretty significant drop. It's comparable to what you with screening mammography, comparable to what the lung cancer screening trial showed, colon cancer screening.

James D. Brooks, MD (guest speaker):

So that's the evidence behind the screening, but that's also why this every other year number came in. It came from what we call Level I evidence, that is, a prospective randomized trial that showed the drop in death rates in a screened and non-screened population. Why every other year? Total number of men diagnosed with prostate cancer is just over 200,000 men per year. The number of men who die of prostate cancer is closer to maybe 28 to 30,000. So that means there's a huge discrepancy between the number of men found to have prostate cancer and the number of men dying of prostate cancer. That's not because we're brilliant and we cure everyone with prostate cancer. It's more reflective of what I alluded to a little while ago, which is the biology of prostate cancer.

Ruth Adewuya, MD (host):

Annual PSA testing was recommended for men over 50 until 2008. Why was this guideline changed?

James D. Brooks, MD (guest speaker):

The current screening guidelines, American Cancer Society recommends starting at 50, the American Urological Association at age 55. Based on that ERSPC trial I just mentioned, the urology guidelines of that, I think 50 is a reasonable time to start screening, and I think every other year is what most people are recommending based on that clinical trial. Prostate cancer is a slowpoke. It's also very common, so prostate of cancer can be very commonly found in men as they age. So a 60-year-old man, if you look and finally dissect their prostate after they die of other causes, you can find cancer in about half of them. Half of men don't die of prostate cancer. It's about 2.8% for a Caucasian male in this country, about 3.6% for an African American. So many men are walking around with prostate cancer, only a small fraction die of it. Why? Because many prostate cancers are so slow-growing, a man would've to live to 150 years old for it to catch up to him. So that's why you start screening relatively late in life, age 50, because that's where most prostate cancer happens, and only every other year.

Ruth Adewuya, MD (host):

I'm curious if there are any instances where you would still screen someone on a yearly basis. Are there any indications?

James D. Brooks, MD (guest speaker):

That's a really important question. The first is African American men. They not only have slightly higher rates of getting prostate cancer, they have significantly higher rates of dying of prostate cancer, almost double of Caucasians. And because of that, we usually recommend screening in an African American man at about age 45, I think is a very reasonable time to start screening. If that man has a super low PSA, it's okay to wait a couple years before you check it again. But once they hit age 50, I think yearly PSAs is appropriate. That's what many guidelines recommend. So too men with a family history of

prostate cancer, that is, prostate cancer in a direct family member: a brother or a father. These can be genetic types of prostate cancer, and up to 5 to 10% of prostate cancer can be hereditary in nature. Those men deserve and need to have more frequent testing, yearly testing again. And again, probably starting at age 45 is a very reasonable time. That's what many of the guidelines recommend.

Ruth Adewuya, MD (host):

Is there a discussion... Are there race-specific ranges for PSA, or is it simply what you just said, we know that African American men are at more risk, and so we screen earlier? Or are there other specific ranges?

James D. Brooks, MD (guest speaker):

We really use the same cutoff for everyone. It's just easier to remember. There are some population studies that suggest African Americans have slightly higher PSA levels. They also have slightly higher level of prostate diseases, not just cancer. So just keep it simple. Use the same number, that cut off of four in the United States, as a sign of abnormality. That is, maybe this is someone that you need to refer to a urologist.

Ruth Adewuya, MD (host):

On the flip side of my question to you, "Do we do it frequently or earlier," is there a point in time where one recommends discontinuing the screening?

James D. Brooks, MD (guest speaker):

Yeah, and that gets at what we discussed earlier, the biology of prostate cancer. It's so slow-growing. That randomized trial in Europe, the ERSPC PSA testing, did demonstrate that men after the age of 70 didn't really benefit from PSA testing. Now, I think there's a gray zone there, myself. Virtually every screening guideline committee will recommend stopping PSA testing at age 75. The gray zone is 70 to 75. If you have a super healthy man who is 72 years old, it's not unreasonable to get a PSA test, but I usually recommend stopping at age 70. Certainly, that's what I'm personally going to do. Age 75 everyone agrees is time to stop screening for prostate cancer.

Ruth Adewuya, MD (host):

As you were talking about the evidence behind PSA testing and screening, it occurred to me that interpreting a PSA result seems to be quite complex when you take in certain factors. How would you communicate PSA results to primary care physicians who might not be familiar with the details of the test, the sensitivity, specificity, the risk of false positives and negatives? How would you communicate to primary care physicians? And then my second question is how would you communicate that to patients as well?

James D. Brooks, MD (guest speaker):

A hard question. What I usually tell patients or physicians is that PSA is pretty sensitive in terms of picking up cancer. Let me give you an example. If you take a man who has a PSA greater than four, and you look at all the guys who have cancer that you're going to find on a biopsy out there, a PSA greater than four will pick up 85% of them. So 15% get missed. Who are those 15%? Most of them have these small, low-grade autopsy-type cancers that are missed. It's rare to miss a really aggressive type of prostate cancer when the PSA is less than four. So in terms of sensitivity, it's pretty... Specificity, I already alluded to. That is, if you have an elevated PSA above four, 75% of the time, the cause is

something else. Most commonly, it's due to benign prostatic hyperplasia, or BPH, which is enlargement of the prostate.

James D. Brooks, MD (guest speaker):

Virtually every man gets an enlarged prostate for whatever reason. After age 40, 50, or 60, in all men, a certain part of the prostate, the central region of the prostate that we call the transition zone, named by John McNeal at Stanford years ago... The transition zone takes off growing, and the prostate gets bigger, and a bigger prostate means a bigger PSA. It's cause for false elevation of PSA. A second common cause of PSA elevations is infection. So I very frequently get referrals for patients who have a urinary tract infection, and they happen to get a PSA at the time of that urinary tract infection, and it's a false positive. So I would encourage people to be very careful about measuring PSAs around the time of infection. It can falsely elevate a PSA for up to three months afterwards.

Ruth Adewuya, MD (host):

That was actually my next question: What are the clinically significant causes of elevated PSA? Which you've mentioned just enlarged prostate and infection, among others. In order to reduce unnecessary referrals to urologists, would you recommend then that primary care physicians would just essentially retest, then refer based off of the second one? We know that there's wait times for an appointment with a urologist, and so I think the concern is to get the person to the urologist or the patient to the urologist as soon as possible. I'm just curious what your perspective is on that.

James D. Brooks, MD (guest speaker):

With regard to wait times, remember that prostate cancer is very slow-growing. So it's never an emergency to have an elevated PSA, unless the PSA is dramatically elevated. I've seen PSAs in the thousands, for instance. So that one, you want to get over to the physician. But if it's a PSA between 4 and 10, that's less urgent. You mentioned a very important and interesting point, which is repeating PSAs. There needs to be a little bit of context there, but in many cases, it is a good idea. There was a study done looking at patients who just had come in for different clinical trials, actually a colon cancer screening trial, in which they came in every year or so and left a blood sample. And a research group looked at all of those blood samples and looked at all the PSAs, and found that in about 35 to 40% of men over that 10-year time span, 35 to 40% of the men had a spurious elevation of their PSA.

James D. Brooks, MD (guest speaker):

That is, it suddenly popped up, and then on the next measurement, it went right back down to normal. So you can see these little blips in PSA into clinically significant levels pretty commonly. And so if a physician has a patient who has been tooling along with a PSA of 1.5 for several years, and suddenly it's 4.5, that's a good patient to remeasure their PSA. It certainly could be confirmed, but if it happens to be one of these fake-outs, and on your next measurement a month later is starting to come down, maybe hold off on that referral.

Ruth Adewuya, MD (host):

Moving past the elevated PSA result, if a patient does have an elevated PSA, it's confirmed, it's not one of those fake-outs, what is the decision-making process about whether to take a biopsy?

James D. Brooks, MD (guest speaker):

It depends on the patient. If it's an older patient... And this happens. I get referred patients who have a mildly elevated PSA, and they're 76 years old. I'm very hesitant to biopsy them, because those are patients we probably shouldn't be screening. If it's a patient that has a lot of comorbidities that I suspect don't have a 10 to 15-year life expectancy, I probably am not going to biopsy those patients. Now, those are the more uncommon patients. The common patients that come in have a modestly elevated PSA, many of those we will offer a biopsy. The patients that I might hold off on a biopsy or watch are a couple. The first is not uncommon to see a patient who has a mild PSA elevation that has been right around the same area, the same level of PSA, if you will, for 10 years. They have a PSA of 4.5 for 10 years.

James D. Brooks, MD (guest speaker):

If they've had a stable PSA over that time, that is a very high probability it's due to prostate enlargement, and not due to prostate cancer where the PSA tends to just march along. Patients I will biopsy, patients who really do have a trajectory, or as we call a PSA velocity, that is, the PSA seems to have a steady course in rising every time it's measured, that patient needs a biopsy. Younger men, I'm more prone to do a biopsy. A man who has a relatively small prostate on rectal examination and an elevated PSA has a higher chance of having cancer. Any man who has an elevated PSA who has abnormal rectal examination [inaudible 00:19:44], either by the primary care or by the urologist, if we feel something abnormal on the prostate, they need a biopsy. And then there's tools that we can use to try and rule out men that need a biopsy. There's new tools that have come along.

Ruth Adewuya, MD (host):

Perhaps this is one of the things that you'll mention, but I'm curious if molecular and genomic analysis plays a role in reducing or preventing unnecessary biopsy. What are your thoughts on that?

James D. Brooks, MD (guest speaker):

It's an area that's very much in flux and what I've spent most of my career researching. There are some tools that are useful for determining whether or not a patient needs a biopsy. That being said, there are not many genetic markers that we use to determine patients need a biopsy. Men that carry mutations in the breast cancer genes BRCA1 one and BRCA2, they're at risk for prostate cancer. And particularly patients with BRCA2 mutations tend to have more aggressive prostate cancer, best as we can tell. So if I'm sent a patient with one of those mutations, yeah, that's a patient that a molecular tool is telling me I need to be really careful with that patient, and have a low threshold for biopsy. But aside from that, there's not a lot of other molecular markers. Now, the problem with the genetic markers for the risk of prostate cancer is that they all only very slightly increase your risk of prostate cancer, and there's very many of them.

James D. Brooks, MD (guest speaker):

People are starting to put those together, like sum all these genetic markers together in what are called polygenic risk scores. That might be something that comes down the pike that we use for determining who does and does not need a biopsy. As for other types of tests, right now, there aren't any that we use regularly in the setting of a patient who comes in with an elevated PSA and has never been biopsied before. There's a molecular test called PCA3 that can be used to look for prostate cancer. PCA3 is actually an RNA. It's called a long non-coding RNA, and it's an RNA that doesn't code for a gene that can be measured in the urine. And that RNA, if it's elevated, can mean prostate cancer. The tool was actually developed so that actually, if PCA3 is low, that's where the assay's really tuned.

James D. Brooks, MD (guest speaker):

That is, if it's low, that means there's an extremely low risk of having prostate cancer. So it's better for predicting who doesn't need a biopsy, and that's what we need that tool for. The only other thing I would add to that is I guess it is molecular. There are other forms of PSA that we can use that help us. For example, free PSA has been around since the 1990s, early 1990s. Free PSA is PSA that floats around all by itself. It's not stuck to other proteins. In any event, you can measure total PSA and free PSA. If the percentage of free PSA is very low, that is, less than 10%, there's approximately a 56% chance that on biopsy, that patient will have cancer. On the other hand, if the free PSA is very high, that is the PSA that comes from BPH is very, very high, let's say above 20 or 25%, the chance of finding cancer in biopsy is about 5%.

James D. Brooks, MD (guest speaker):

So that's a tool I use frequently when... Mainly in a man who I'm trying to determine who I should not biopsy, I'll use that tool frequently. Then there's other forms that have come out recently that are commercial kits that combine a couple other proteins with it, but the real workhorse is free PSA. One of them's called the 4kscore. One of them's called the PHI, or PHI, or Prostate Health Index score. Those are also tests that basically are leveraging free PSA to determine whether or not to do a biopsy on a man. So those are kind of it. The final test that's out there is one not used very much, which is again in a man who came in, had a biopsy, no cancer found. It's based on whether the DNA is methylated in specific genes. But that's another molecular tool out there, not a very popular one. There's a few coming down the pike that are really in testing, and it's too early to tell if they're going to work or not.

Ruth Adewuya, MD (host):

Are you excited, though, about any of them as you're looking at early data?

James D. Brooks, MD (guest speaker):

Some of the new ones look pretty interesting. One involves looking at little things that bleb off cells called exosomes. You can not only measure them, but measure their content. If they come off prostate cancer cells, can be used to identify patients at high risk for prostate cancer. We'll see how they work.

Ruth Adewuya, MD (host):

So we've been talking a lot about elevated PSA and how it relates to prostate cancer. Does low PSA mean anything if it's below normal? Does that mean anything related to prostate cancer, or that's not significant?

James D. Brooks, MD (guest speaker):

That actually does mean something. There have been studies that have looked at that, a famous one by a guy named [Peter Gam 00:25:08] who looked at PSA and men in their forties, a single PSA value for men in their forties. And if it was really low below the median, which is below 0.6 for a man age 45, they had a lower chance of ever dying of prostate cancer. People have found similar results in other large groups of patients, that the patients with the lowest PSAs at a younger age tend to have a lower risk of ever dying of prostate cancer. One thing that's come out in the last 10 years that's really changed things is the use of MRI imaging. We've known since the early 1990s can show us things inside the prostate, but now the engineers have made it even better.

James D. Brooks, MD (guest speaker):

So there's a type of MRI called multiparametric MRI which will pick out prostate cancers, and when I say that, the significant prostate cancers, the higher-grade ones, that can go on and shorten a man's life expectancy. Will identify those in up to 90 to 95% of the time. And it tends to not identify those small, low-grade ones that we probably don't want to find, the autopsy-type ones. So MRI is gaining popularity as a tool for identifying men with prostate cancer. The other thing is that you can use that MRI. At Stanford, Geoff Sonn and Alan Thong used the MRIs to actually guide their biopsy. So they have technology that allows them to fuse the MRI image to the ultrasound to do these targeted biopsies, which increases the accuracy of the diagnosis of prostate cancer.

James D. Brooks, MD (guest speaker):

So that's been a sea change in recent years. Now, it's not perfect, so there are some cancers that can be missed on MRI. Just PSA isn't perfect, so too with MRI. The other issue is one of resources. MRIs are expensive. But when they first started gaining popularity, there were insurance plans, and there still are some insurance plans, that won't pay for them in men who've never had a biopsy before.

Ruth Adewuya, MD (host):

Thanks for highlight that, this new advances that are coming up, and even some of what you talked about earlier with the tools that are available. Is there any relevance to primary care specialists?

James D. Brooks, MD (guest speaker):

Right now, I think those tools probably are best used by the specialist. The one exception to that, I think, is I think there are a lot of really outstanding primary care physicians who are good at using free PSA as a tool for figuring out which patients with mildly elevated PSAs they need to worry about, and know the cutoffs and know how to use them. The other thing that's a challenge, that this alludes to, is which of these many tools do you use? And in which order do you use them? And that is not at all clear at this point. We're participating in studies now that are funded through the National Institutes of Health to try and figure that out. So we're collecting blood and urine and MRI scans on patients who come in with an elevated PSA, sending them to a central repository where the research is actually going to be done by a variety of groups, including us, trying to figure out...

James D. Brooks, MD (guest speaker):

Do we do that PCA3 test? Do we do the molecular forms of PSA tests, free PSA tests? Do we do those first? Do we just go right to an MRI? How do we sequence these tests to get the most information? That's something that's wild west right now in urology, trying to figure that out. And we have to figure it out, because again, we have to be using our resources responsibly. Again, I have patients come in who have all of the tests done many times, with contradictory results. And then what do you do? So coming up with the rational sequence of using these is going to be really critical to managing patients with elevated PSAs, and effectively screening for prostate.

Ruth Adewuya, MD (host):

Yeah, absolutely, and something to look forward to, hopefully, as more research is done in the field. I wanted to pivot a little bit. We've been talking about prostate cancer generally, but as anyone looks into prostate cancer, some terminologies come up. And help us define it, or explain it further. Some of the things that I see is castration-resistant prostate cancer versus castration-sensitive prostate cancer. Are you able to unpack that for us and elaborate on some of the similarities or differences?

James D. Brooks, MD (guest speaker):

Yeah. Actually, it was in about 1941 that a urologist named Charles Huggins published an article showing that prostate cancer depends on the male hormone testosterone to grow. He was one of two urologists to win the Nobel Prize for his discovery of both prostate and breast cancer depending on steroid hormones to grow. So castrate-sensitive prostate cancer is prostate cancer that still responds to testosterone, the male hormone. So this would be what virtually every localized prostate cancer is that's diagnosed. It's also men who come in with more advanced prostate cancer. There's some men that have never been screened and they get their first PSA, and it's 300, and they have prostate cancer that spread to the bone. That prostate cancer still responds to taking away testosterone, which we do now with various drug. Castrate-resistant prostate cancer is cancer that occurs in men who've been treated with anti-hormonal therapy, or therapy that blocks testosterone either from being made or from binding to and getting into the cancer cells.

James D. Brooks, MD (guest speaker):

And there's various drugs that do each of those things. So prostate cancer is devious. And so after depriving it of testosterone, the cancer acquires methods of growing without testosterone, i.e., it becomes castrate-resistant. And there's a bunch of ways it does it. It makes more of the receptor, that is, the thing that by testosterone. It mutates the receptor, so it can accept other hormones. Some prostate cancers make their own testosterone, believe it or not. So there's a variety of ways that prostate cancer escapes androgen deprivation, or castration, in order to grow.

Ruth Adewuya, MD (host):

Would it be an appropriate synthesis to say that this is a progression that prostate cancer goes from being sensitive to resistant?

James D. Brooks, MD (guest speaker):

Absolutely, yep. That is a progression. It's a progression of response to treatment. Cancers evolve to keep going, unless we can cure them, and that's the idea with screening. We find them early and take them out.

Ruth Adewuya, MD (host):

Before they become resistant.

James D. Brooks, MD (guest speaker):

Yeah, so they don't have a chance to further evolve to evade our therapies. That's why many advanced cancers are so dire, is because they have abilities to evolve and escape therapies.

Ruth Adewuya, MD (host):

In this conversation, I've also taken away that prostate cancer is a slowpoke, but also devious. And so-

James D. Brooks, MD (guest speaker):

Yes, yeah.

Ruth Adewuya, MD (host):

[crosstalk 00:32:28] that's also a great summary.

James D. Brooks, MD (guest speaker):

Yeah, yeah, yeah. That's true. Let's say a patient has an elevated PSA, and we do a biopsy, and we take 12 samples, and 6 of them have cancer. What are the things that the urologists or the radiation oncologists, whoever, looks at? The first thing is the stage of the cancer. If the cancer is just within the prostate, that is, when we do a rectal exam we don't feel it growing through the edge of the prostate, maybe we do some imaging. So if a patient comes in with a very high PSA or if they have very high-grade cancer, and I'll talk about that in a second, and we do some imaging, we don't see any signs of spread of cancer to the bone, which is one of the more common places advanced prostate cancer goes, or to elsewhere in the body, such as the lymph nodes...

James D. Brooks, MD (guest speaker):

Those are the two common landing sites for prostate cancer, bone and lymph node. So if we don't see any sign of that, we stage the prostate cancer based on where it is in the prostate. So if the prostate feels normal, it's a stage T1. If we can feel a lump on the prostate, it's stage T2. If the prostate's growing out through the edge of the prostate or up into the seminal vesicle based on imaging or rectal exam, it's a T3. If it's invading other organs, it's a T4. Advanced-stage prostate cancers, metastatic prostate cancers, people sometimes use different numbering schemes and so on, but it's basically if it's in the lymph nodes, it's N1 or N2. If it's metastatic disease and it's not very much, it's an M1. If it's more, it's M2. That's really critical to figuring out how we're going to treat the patient.

James D. Brooks, MD (guest speaker):

The patients that have localized prostate cancer, namely the ones with T1 or T2, are ones that respond well to local treatment, just treating the prostate. If it has gone out into the tissues around the prostate or into local lymph nodes, probably radiation therapy is more appropriate for those patients. It's hard to cure those patients with an operation. If the cancer is spread distantly and to many lymph nodes or bone, or to things like soft tissue, like the liver or lung, then they have advanced prostate cancer, and they should receive systemic therapy. That is, usually we start with some type of hormonal therapy. These days, it's combined hormonal therapy. That medical oncologist can tell you more about that. I think you're going to do a series. And so stage is absolutely important. The other thing I alluded to is grade, the grade of the cancer. Because the grade we've used typically is what's called Gleason grading, named after Don Gleason, who was a pathologist at the Mayo Clinic.

James D. Brooks, MD (guest speaker):

And the way Gleason grading works is it basically looks at how the cancer cells are arranged at low power view under the microscope. In other words, if they are nice and organized little circles of cells with hollow middles that look a lot like normal prostate glands, they get a score of one, two, or three. If they start becoming disorganized, fusing together, they get a score of four. If they're completely disorganized sheets of cells, a score of five. These days, no one really calls pattern one and two anymore. The lowest score handed out is three, for practical reasons. They behave the same. They're all real slowpokes. And second of all, if you ask pathologists, you'll get a different answer from every pathologist of whether it's one, two, or three. So by practice now, Gleason scoring is either pattern two, three, or four. So Don Gleason also recognized that many prostate cancers have more than one pattern.

James D. Brooks, MD (guest speaker):

It's fairly common to see pattern three mixed with pattern four, and so he decided to just add the two most common patterns together. What we have learned since Don Gleason's time is that three plus

three and below are all slowpokes, though many of those we manage by watching them. For pattern three plus four and four plus three, Don Gleason regarded those as a single entity. We now know that three plus four is less aggressive than four plus three, and we might manage those differently. Four plus four is more aggressive. Anything with pattern five, four plus five, and five plus five are quite aggressive, have a pretty high probability the cancer's escaped the prostate. So this Gleason grading provides us really important information.

Ruth Adewuya, MD (host):

It sounded to me that the specialty group is really the one that is responsible for the staging and the management of treatment of the prostate cancer patient. Is that correct?

James D. Brooks, MD (guest speaker):

That is correct, yeah. And usually, the first contact point is the urologist, because they're the ones who are dealing with the elevated PSA patients, do the biopsy.

Ruth Adewuya, MD (host):

In the continuum of care of a prostate cancer patient, is there a role for the primary care physician? Obviously, they're the ones seeing them and doing the screening and then referring. On the backend or during the treatment process, is there a role for the primary care clinician?

James D. Brooks, MD (guest speaker):

There is. The role for the primary care physician in patients with localized prostate cancer is complicated. It is very common for patients to go back to their primary care physician, who they've known a long time and trust, and say, "Look, this urologist is telling me this. I need an operation or I need radiation. What do you [inaudible 00:38:04]?" This is very common that this happens? So the primary care physician needs to be familiar with the different treatments that are out there, and familiar with the fact that there's some controversy over which treatment is the right treatment.

Ruth Adewuya, MD (host):

I'm curious, what's your take on this?

James D. Brooks, MD (guest speaker):

My take on which treatment is the right treatment is that best as we can tell, surgery and radiation therapy both work. This has not been tested yet, believe it or not, in a prospective randomized trial. That is, we have not taken patients with localized prostate cancer, tossed a coin, they get surgery or they get radiation therapy. Let's see how they do. There's only one study that's done that to any degree that I really trust. It's a trial called the ProtecT trial, done in Great Britain. The problem with that study is that most patients had low-risk prostate cancer. 77% had Gleason three plus three, or what we now call Grade Group 1 prostate cancer. Those are patients I would recommend surveillance. I'd recommend watching them. And what we found from that trial is that if you compare surgery to radiation therapy to surveillance, which was done in that study, no matter what, you had less than 1% chance of dying of prostate cancer 10 years later.

James D. Brooks, MD (guest speaker):

There was a little bit more progression of the cancer in the patients who were watched compared to surgery and radiation therapy. The protection both surgery and radiation afforded was comparable. People have done big studies in which they've tried to compare apples to apples, that is, patients with the same Gleason score, same stage, everything similar on biopsy with surgery and radiation therapy. The answer that you almost always get is that the outcomes are identical if you look 5, 10 years later with surgery and radiation therapy. So best as we can tell, they're comparable. Both have their own set of side effects, and that's the other thing that determines patient decision-making. So incontinence with surgery, urinary bother with regard to urinary frequency and urgency with radiation therapy, just due to the effects of radiation on the prostate and bladder.

James D. Brooks, MD (guest speaker):

Radiation has some unique things. It has rectal bother, so loose bowel movements or blood in the bowel movements. Blood in the urine comes from radiation therapy. Those are things you don't see with surgery. So all these things need to be factored into making these decisions. Patients come and talk to their primary care physician about it. So the more that the primary care can know about this, the better. But it is a very frequent source for long conversations for me in clinic to try and explain this in detail to patients to help them make an informed decision, about what is the most appropriate course for them to take.

Ruth Adewuya, MD (host):

What I hear from you is underscoring the need for our primary care clinicians to remain up to date and aware of what's happening in the world of prostate cancer treatment, because they are often asked by their patients. And their knowledge allows them to work alongside the specialists to encourage the patients to take the best action possible, based on the evidence that you have. I'm pleased to hear that, because I think especially for this podcast, I can imagine the challenge that primary care clinicians have just navigating those different treatment options, what's happening in the midst of the 17 other illnesses that they're trying to manage as well.

James D. Brooks, MD (guest speaker):

Oh, yeah. Yeah, it's a real challenge. The other help that a primary care physician often gives is following patients afterwards. Now, many of us, when we operate on patients will follow up with our patients and check PSAs. After surgery, the PSA should go to undetectable levels, that is, below the levels of detection offered at your laboratory. That can be less than 0.1. It can be less than 0.05, whatever assay's being used. But many patients just go back to their primary care physician. If their PSA is staying undetectable, they're fine. They're for all intents and purposes cured. I have seen it happen where patients develop a detectable PSA, and it does get missed just because the way PSA is reported out is... There's a normal cutoff of four in a PSA that starts rising. It's not right to have any detectable PSA after an operation, so PSA that goes up to one is one that needs to be referred back to a urologist. In fact, any detectable PSA, I don't care how low, if it's measurable, should be referred back to a urologist for management of that patient after surgery.

Ruth Adewuya, MD (host):

Great points. As we wrap up this conversation, I would ask you, any last thoughts or insight that you can share with primary care clinicians that are managing prostate cancer patients in their respective clinics?

James D. Brooks, MD (guest speaker):

I think we already hinted that things are still moving along, and there's new types of scans coming out, including PET scans that can show things even better than MRI in the prostate. That's going to change the field. The final thing is in advanced prostate cancer, what we have done in the advanced space since I started, where all we had was castration or a drug called Lupron, to now is dramatically different and dramatically improved in terms of prolonging patients' survival. I'm very hopeful, and I think that we're going to continue to make a ton of progress in prostate cancer, and we just got to keep researching a way to do it.

Ruth Adewuya, MD (host):

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