[MUSIC PLAYING]

BRUCE JACOBS: It's quite an honor for me to be here today talking about prostate cancer screening and management. This is very much what I think about on a daily basis. It's a good proportion of my clinical practice, and also my researches in this area.

The most challenging thing is this could be a topic for a whole-day conversation. But I'll keep this brief, to about 20 minutes or so, and then I'll be happy to answer any questions.

So I think a good place to start this discussion is with the recommendation by the United States Preventative Services Task Force back in 2012 that looked at prostate cancer screening with the PSA test and recommended against screening. And this recommendation applied to all men in the United States regardless of age. And again, it was Grade D, which means do not screen.

And so I wanted to go over a couple of the pivotal studies that this recommendation was based on. And so the first was this study out of the United States, the PLCO trial. And this was published in *The New England Journal of Medicine* back in 2009. And this study was from 1993 to 2001, and it was a randomized trial where they looked at about 76,000 men to receive annual screening with PSA tests or what they called usual care, which was the control group.

And this is the main finding from that paper, which looks at prostate cancer mortality and-- sorry, there we go. And there was no difference in mortality among the patients that had annual screening and the control group, and the follow-up ranged from about seven years to 10 years of follow-up.

And in the same issue of *The New England Journal* back in 2009, there was another randomized trial that came out of Europe. This study was a little bit larger. iT randomized 182,000 men from the ages of 50 to 74 to PSA screening at an average of once every four years-- so not as rigorously as the screening study in the United States. And then there was a control group that did not receive any screening. And this involved about seven countries in Europe.

And this is the main figure from that study, which basically shows lower prostate cancer mortality in the screening group. The follow-up in this study was a little bit longer. And as we can see, these curves don't really start diverging until about nine or 10 years of follow-up, and then by year 14 they're further apart. And so one difference between this study and the United States study is that there is a little bit longer follow-up.

And the conclusions in this study was that screening reduced the rate of death from prostate cancer by about 20%. But there was also a risk of over-diagnosis and over-treatment. So they estimated you had to screen about 1,400 men and you had to treat about 48 men to prevent one prostate cancer death.

And so this obviously created a lot of comments when the task force came out with the recommendation not to screen for prostate cancer. This is an editorial out of JAMA that says that this was missing the mark. *The New York Times* came out with an editorial-- should we be screening, should we should we not be screening?

And there are a couple reasons why this was debatable. So this is looking at mortality by different sites. And prostate cancer mortality decreased by 40% over that time period since PSA came about. And PSA came about late 1980s, early 1990s. And so some people point at this is an argument. Well, we shouldn't be getting rid of screening altogether, because of this decrease in mortality.

Other people point to some of the things in these two trials. In the PLCO trial, one of the biggest criticisms was that in this control group about 50% of patients were screened with PSA. And so one of the arguments is you're really comparing people that were screened to people that were screened a little bit less.

Another comment was that the task force that made the recommendation by intention didn't have people who would be biased-- such as urologists, radiation oncologists, or medical oncologists-- so none of these people were involved in looking at this literature and making the recommendation.

As a response, our organization, the American Urological Association, went back and reviewed all the literature as well, and then they changed their screening guidelines as well. And they concluded that in men aged 55 to 69, they should be offered biennial screening in a setting of shared decision-making. So it's a topic that should come up with patients to discuss potential risks and benefits of screening.

Men under 40 or over 69 years of age should not be routinely screened. The thought is that the risks of screening outweigh the benefits, and that evidence was insufficient to recommend screening and men in this 40 to 54 age bracket.

I wanted to touch base on this article that came out within the last couple of weeks. This is a group out of Britain looking at 10-year outcomes of monitoring, which is considered conservative management or active surveillance, surgery, or radiation for patients with localized disease. This study accrued patients from 1999 to 2009 and randomized about 1,600 men with localized disease to active surveillance, surgery, and radiotherapy, a little over 500 in each group.

And the first take-home message from this study is that prostate cancer mortality in general for patients with localized disease is low. Especially within a 10-year people, most people with prostate cancer will do very well and they'll likely die of something else. They then compared the mortality between these three groups, and in this 10-year period there was no difference in survival. And this was a follow-up of a medium of about 10 years.

They also looked at what they called freedom from disease progression. So this includes things such as metastatic disease. Also, the need for additional therapies for advanced localized disease. And this is thought to be potentially a marker of prostate cancer mortality several years down the road. And in this analysis, surgery and radiation was associated with lower rates of disease progression and metastasis than was active surveillance.

Before I get to some cases, this study which just came out really has something for everyone in the sense that it clearly shows that for patients with localized disease, active surveillance is safe. Survival is very high, out to 10 years. It also shows some findings of increased metastatic disease in this population.

And so it's important for us to think about how old is the patient, how healthy are they, and how long do we think they're going to live, because we haven't been doing active-- we have good data showing that active surveillance is safe with 15 years of follow-up. But active surveillance hasn't been around much longer than that, so we don't know what happens 20, 25 years down the road.

So I wanted to present a few cases to kind of emphasize some points, things that you might see in your patients in clinic and wonder what to think about it, and then I'll give my two cents on how I approach these patients.

So case one is a 65-year-old-- these are all men-- PSA 6 and 1/2. Did a biopsy, and the report comes back with high-grade PIN, high-grade prostatic intracellular neoplasm, intraepithelial neoplasm in three of 12 cores, and something called atypical glands in two out of 12 cores. And this person's otherwise healthy.

We see this report not infrequently. The easiest way to explain this to patients is we basically tell them this is a precancerous lesion. You do not have cancer. This isn't cancer. But when we look at patients that have this on their biopsy compared to patients who have a completely negative biopsy, there is an increased risk that you will have developed prostate cancer sometime in your lifetime. And the risk is higher with these atypical glands than they are with high-grade PIN.

And so the options when I see patients with this on their biopsy is I talk to them about whether we should repeat a biopsy to make sure that we're not missing anything more significant than these precancerous lesions. But more so in the last few years, we've been able to recommend an MRI of the prostate.

This has really helped us change the way we think about prostate cancer and has reduced the number of biopsies that we do. It's a way to image the prostate and see if there are lesions within the prostate that look concerning for cancer. On a lot of cases, we can avoid doing a repeat biopsy if these MRIs look OK.

So in this patient, I will often get an MRI with the idea that if there is a lesion concerning on the MRI, then we will proceed with a biopsy. But now we have the technology where we can actually fuse the MRI with our ultrasound image so that we can target specifically the lesion of concern.

Next case, again, is a 65-year-old, PSA 6.5. Gleason 3 plus 3 equals 6 in two of 12 cores. They will often tell us what percent of the core is involved with cancer, to give us some idea of how much cancer is in the parts of the prostate that we can't sample. And this patient is otherwise healthy.

And so one of the options is active surveillance. Another is surgery. Another is radiation. So I wanted to take a quick poll of the room. Who thinks this patient would be a good candidate for active surveillance? Good, decent number. How about surgery? And radiation? Good.

So there's not a wrong answer here. I would say 15 years ago-- again, active surveillance wasn't really around, so this patient would have received surgery or radiation. No matter what this patient gets, this patient's going to do well, at least in the foreseeable 10 to 15 years, because this is a low-risk disease and there's not much of it.

And active surveillance, which is what I would push for in this patient, is a totally reasonable option. And I tell patients, it's not that we're not going to follow you. we're. Going to actively follow this closely. So there are a lot of different algorithms, but one of the common ones is we'll get PSAs and a prostate exam every six months, and we'll get a biopsy or an MRI every year for the first several years up to about five years, and then we'll start to space things out to maybe every other year, just to make sure that things don't change.

And by doing this, this is a way for us to try to avoid over-treating these patients. Because historically, we've been over-treating these patients, which has its risks. And I think in large part, that is what has led to the strong voice against screening altogether for this disease.

Active surveillance isn't for everyone. So if I say I strongly suggest you get active surveillance for this low-risk disease-- it's not going to kill you-- some patients will be crying hysterically and say, I cannot possibly live with this diagnosis of cancer and I need something else. And so we will talk about the more aggressive treatments, but really just highlight the fact that it's associated with more risk than active surveillance.

Next case-- so 65-year-old, PSA is 6.5. Biopsy shows Gleason 3 plus 4 equals 7 in six of 12 cores. Maximum involvement 50% of the core, and this patient is otherwise healthy. Anyone would choose active surveillance for this patient? Surgery? And radiation?

Yeah. So I wanted to go over this case for a few reasons. One is I would agree that this is not a good candidate for active surveillance. So one of the conversations we often have with patients who come in with this picture is, well, I didn't need to be screened for this and I'm not going to die from prostate cancer, so I don't see any reason why this needs to be treated.

And although there's some truth to prostate cancer being a slow-growing cancer-- and active surveillance has its role for some patients-- I would argue that with a Gleason 7 disease, especially in someone who is otherwise fairly young and healthy, it would be too risky to follow this person on active surveillance.

I generally would follow Gleason 7 disease only in patients who were not healthy, or over 70 or had low-volume disease. In my mind, right now you're taking the risk with active surveillance of having a cancer that could be completely cured with aggressive treatment. And you're taking that risk that while you're watching, this could progress.

And the one thing with prostate cancer is that once it spreads outside the prostate to other parts of the body, we don't have very good treatment options. There's no cure. We have some treatments. They don't work very well. And so in my mind, if you miss an opportunity to treat localized disease and someone then goes on to progress to metastatic disease, that's not good.

As far as surgery or radiation, I think either one is totally appropriate in this patient. I will tell patients that we don't have great evidence with head-to-head trials of surgery and radiation. But the outcomes from a cancer control perspective for this patient are going to be about equivalent if you get surgery or radiation. Either way, your chance of being disease-free at five years is about 80%, 85%. And after five years, your chance of recurrence really goes down.

And so at that point the discussion transfers from, OK, you have these two different treatments which are completely different from each other with essentially equivalent cancer control. And then we go over the different side effects. And there are many, and they're very different between surgery and radiation.

And so the things that I will focus on with surgery-- there are two main side effects that we need to talk to our patients about. One is urinary incontinence, or leakage. And that's because the urethra goes right through the prostate, so when we remove the prostate we have to cut through the muscles there and then reattach the bladder to the remaining urethra. So we talk about the risk of incontinence.

And then we also talk about the risk to erections. The nerves that control erections go right alongside the prostate. In all cases, we try to spare the nerves. We can do so roughly 80% of the time. I do tell patients, obviously it's a cancer operation first, so we're going to err on taking some of the nerves if we feel that there's cancer encroaching on the nerves on that side. But at any rate, the two main things we talk to patients about who are considering surgery in this situation are the urinary incontinence and the erectile dysfunction.

On the radiation side, we don't really have to worry so much about urinary incontinence. There are other side effects with radiation, namely irritative urinary and voiding symptoms that often come up. And those can be exacerbated in people who have particularly large prostates, so we have to be a little more careful giving radiation in that setting.

Erections initially are not really affected. But eventually with radiation they are, because the nerves are in the field that gets irradiated. There are some other, less-common side effects with radiation. Sometimes we see patients back who have bleeding in their urinary tract from hemorrhagic cystitis, which fortunately is uncommon. Unfortunately, it's very hard to treat.

And then there's a remote chance of secondary cancers, but that's usually about 15, 20 years down the road. So as patients get older, we don't really worry as much about that.

So as far as the distinction, surgery versus radiation, it's very much a two-way conversation. It's a case-by-case basis based on patient preferences and that sort of thing.

I'll also touch base just a little bit with the surgery. There are two different approaches to surgery. So who in this room-- so there's an open prostatectomy and there's a robotic prostatectomy. Who here thinks that the robotic prostatectomy has better outcomes than an open prostatectomy?

Yeah. I mean, this is a little bit of a trick question. I mean, that is definitely the--

SPEAKER 2: Joel gave the lecture last year.

BRUCE JACOBS: Oh, OK. So Joel Nelson is my boss. He also taught me how to do a prostatectomy, and he's done about 3,000 open prostatectomys.

But yeah, the robotic prostatectomy came about in the early 2000s and really caught on like wildfire. Now I'd say about 85% of prostatectomys are done robotically.

And part of my research interest, actually, is studying kind of why this diffused as rapidly as it did. And I do think there are some advantages, in some ways, with robotic prostate. But what's interesting about it is, despite it having really taken over as the surgical approach, there aren't really any studies that have really shown that it's any better than the traditional open prostatectomy, certainly as far as cancer control-- and, you can argue, based on side effects. The one thing you can't argue is that robotic prostatectomys do cost more. The robotic is expensive.

My training, I came up in an era where when I first started my training there was no robot. So it was all open prostates. And then by the end of my training, it was a lot of robotic prostates. So I do them both ways. And this is someone that I'd feel comfortable doing either with an open or robotic approach.

And I think that the real answer to the question of whether this person should have a robotic or an open prostatectomy has more to do with the person who's doing the procedure. So if the person feels most comfortable doing an open approach, then I would recommend going with that approach. Whereas you don't want your open surgeon doing a robotic prostate, and vice versa. You don't want your robotic surgeon doing an open prostate. So it has a lot to do with surgeon comfort in that situation.

But just as an aside, we still do a lot of open prostates here at the University of Pittsburgh, more so than a lot of places in the country.

OK, last case-- 65-year-old, PSA of 12. Gleason 4 plus 5 equals 9 prostate cancer in six out of 12 cores. Maximum involvement 80%. This person by definition has high-risk disease. Anyone with a Gleason 8 or higher has high-risk disease. And in those patients, we tend to get a CT scan and a bone scan to make sure that they don't have any disease outside their prostate. Otherwise healthy.

I'm going to touch base a little bit on the screening aspect here with the CT scan and the bone scan. Prostate cancer in general has a very low risk of spreading outside the prostate. And when it first spreads, it's going to be microscopic.

And so the thought is that patients with low-risk disease-- unless someone has a high alkaline phosphatase or complaining of bone pain or something really kind of out of the ordinary-- we never get a CT scan or a bone scan in those situations, because they're never going to show something that's prostate cancer.

What it is going to show a large percentage of the time are these indeterminate lesions that you then have to go down this chasing game where you then have to get plain films and MRI and sometimes a biopsy. I mean, so I really try hard-- and I know general consensus is unless the patient has high-risk disease, we really try to shy away from getting imaging to look for disease outside the prostate.

For high-risk disease, I personally always do, just to make sure there's not some bulky disease that we're not taking into account.

So for this patient, active surveillance is not an option. If this patient were 85, then you could talk to them about something called watchful waiting-- which is basically, we're not really going to do anything unless you become symptomatic. But active surveillance is not an option here. So really, the choice here is between surgery and radiation.

And for high-risk disease, unlike people with intermediate risk disease, I do think that there is an advantage for surgery over radiation. Again, there is not really any good head-to-head trial that's going to say, oh yeah, that's true. But there is some evolving evidence that would suggest that the outcomes in this situation with surgery may be better than with radiation.

What I tell patients when I see them with high-risk disease is that-- and these are people who had negative bone scan and CT scan-- is that if we do surgery, the chance of being disease-free at five years is about 50%. So that does mean, even with surgery, there's a 50% chance of meeting additional treatment.

If you were to need additional treatment-- if we thought that your disease was recurrent locally where your prostate used to sit-- then we would talk to you about radiation to that area. If for some reason we thought that the disease had spread to other parts of the body, then we would not give localized treatment but we would wait for a little while and then give something called androgen deprivation therapy, which helps treat disease in other parts of the prostate.

What I like about surgery with high-risk disease is one, we do a lymph node dissection on everyone. And so we will know, is their disease in the lymph nodes or not? And we know now-- what we didn't know before is that even if someone has disease in their lymph nodes, there's a 20% chance that they will not need additional treatment.

So we did not think that before. Before, we thought if there's disease in your lymph nodes, then that means you definitely have microscopic disease elsewhere, and this is not curable. Although that is true the majority of the time, we now know that there's a one in five chance you won't need any additional treatment. And so that to me is a big potential advantage.

We also want to know the true extent of disease within the prostate when we do surgery, instead of just basing it on the biopsy, which is just a sample of the tissue. And radiation after surgery is a very effective treatment if needed. If you do radiation up front, you won't know for sure-- you're guessing that there is not disease in the lymph nodes, but you don't know. You're basing that on a CT scan.

And then I always tell patients, it's not that we can't do surgery after radiation. It just, it's a very morbid procedure. If you take out someone's prostate after that area's been irradiated, things just don't heal well. So your rate of leaking urine is 50%, which is really unacceptable.

So sometimes we do do surgery in that situation-- it's called a salvage prostatectomy-- but very, very rarely. You have to meet very strict criteria. So for those reasons, in these high-risk patients I do prefer surgery over radiation.

And so how can we improve prostate cancer screening and management? There's definitely room for improvement. It'd be nice if everyone we treated we knew needed to be treated, and thus kind of reduce the chance of unnecessary morbidity.

There are a lot of things on the horizon. And I'm not going to go into too much detail, but just to kind of go over a few of these things-- there are a lot of new biomarkers and genetic tests out there, and I've listed a few. There's prostate health index, a four-case score. There are urine tests-- the PCA 3, TMPRSS2-ERG.

And then something that's gotten a lot of aggressive advertisement is the onto type DX test. That's a test where you send the biopsy samples off to a genetics lab and they run some tests and then spit out a score to say what's the likelihood that you're going to have significant cancer.

I touched base already on imaging. I really am a big fan of prostate MRI, if it's used appropriately. And I think this has helped us appropriately select patients for active surveillance and treatment. And I think we're going to start to see this be used more and more in the management of prostate cancer.

It will help us with better patient selection-- again, choosing the right people for active surveillance and choosing the right people for more aggressive treatment.

And obviously, we always strive for better surgical technique and radiation delivery. And I think that has improved over the last-- certainly since I've been in training, and I'm hoping that over the next 10 years we see similar advances in our approaches to the more aggressive treatment.

And shared decision-making-- there's a lot of conversation back and forth with patients about what's best for them.

I left my contact information. Please email me with any questions. Again, it was a pleasure to talk today, and I'd be happy if there's time to answer any questions. Thank you.

[APPLAUSE]