Darryl Mitteldorf: Today we're gonna be talking about radiation therapy for prostate cancer in general and then we're going to talk about why Cyberknife seems to be the next big thing, even though it's been around for about nine or ten years. But I think more and more patients are becoming savvy to considering Cyberknife analogous perhaps to the Da Vinci robotic surgery that many newly diagnosed prostate cancer patients use. So, welcome.

Seth Blacksburg: Thank you so much.

Darryl Mitteldorf: Yeah. And very grateful for you to be here. Let's get into this.

Seth Blacksburg: Sure.

Darryl Mitteldorf: First let's get into what is radiation?

Seth Blacksburg: Radiation is high energy x-rays. So you're deposing energy into a target, and by doing that with the latest technology you're able to kill off a tumor and you're able to preferentially address a given region and to spare the adjacent tissues around that region. That would be my summary of what radiation is. It's a broad question because there's different types of radiation, but in a therapeutic sense the type of radiation that we gave as radiation oncologists is essentially high dose energy that gets delivered to ablate and kill off tumors.

Darryl Mitteldorf: So the kill off part, what are we killing off? How are we killing something with radiation?

Seth Blacksburg: The mechanism, the way that the radiation's working in the classical way, the way that was studied in the 1970s, 1950s, is that it's damaging the DNA of a cancer cell. So when cancer cells try to divide they die off after having radiation. There are theories, and you can really delve into this and there are people who have entire carriers devoted to what's called radiation biology where they ask questions, do larger doses have a different mechanism of action? But essentially the way radiation works in our modern conception of it is that it's killing off the cancer cells through damaging their DNA.

Darryl Mitteldorf: And damaging DNA does what?

Seth Blacksburg: When cancer cells try to divide, which is all that cancer cells do, they essentially die off.

Darryl Mitteldorf: So I think a common thought around cancer cells is that cancer cells divide and continue to divide because the DNA within them is different.

Seth Blacksburg: Sure. The DNA is mutated. Our cells, we have cancer cells throughout our lifetime and our body has a pre-programed way of killing off abnormal cells. The cancer cell is the cell that got away. The body did not realize it was abnormal and that particular cell continued to divide and continued to divide. So the normal process of the body saying, "This cell's not behaving the way it should." It fell through the

cracks. The damage that the radiation performs on the cancer cell DNA is what's called double stranded DNA breaks. It's a fancy way of saying the damage renders that cancer cell unable to continue to divide, and when it tries to it dies off. Again, there are fancy ways of talking about it, the classical way was mitotic catastrophe, which is a very dramatic way of characterizing it. But essentially the cancer cells are dying off and the normal tissue is healing itself in between each of the treatments.

Darryl Mitteldorf: But it's not possible for the cancer cell to heal itself?

Seth Blacksburg: Exactly.

Darryl Mitteldorf: Okay.

Seth Blacksburg: Not with the doses we're giving. So again, radiation's been around for well over 100 years, and it's not a binary thing where you turn on a switch and there's radiation. You're able to really modulate. You're able to really [inaudible 00:04:05] the doses and determine what doses to give, and to what areas you're delivering it, with such accuracy you're able to give the appropriate dose for the appropriate cancer. And not every cancer requires the same dose, and not every normal tissue repairs the same way. So really radiation oncologists, we are practitioners as you had asked, but we're clinical oncologists. We have to memorize what doses every single structure in the body can tolerate, what percentage of whatever structure can tolerate with each dose, and that goes part into the training of being a radiation oncologist.

Darryl Mitteldorf: So different bodies would take different ... Like a skinny guy versus a fat guy?

Seth Blacksburg: No, different structures. So the tolerance of the rectum is different than the tolerance of the bladder. The tolerance of nerves is different than the tolerance of brain tissue. So every structure of our body has a different amount of radiation it can receive and repair itself when it receives from one another. Usually not between individuals.

Darryl Mitteldorf: Not to get too deep into med school stuff, but what is the difference? What is the quality of difference? For example, is the DNA of bladder cells different than prostate cells?

Seth Blacksburg: Each of our structures has a different ability. Each of the organs and systems that we have in our body have a different ability to repair itself when it's faced with what's called ionizing radiation, just high energy. Cancer cells have damage to their DNA, normal tissue, it repairs. You regenerate, you replenish normal tissues. There are lots of mechanisms of the body that constantly ... Think about when you have a burn. When you go outside, you have a burn, you don't stay with that burn forever. Your body heals itself. Think about when you have a cut, your body heals itself. If the cut is too big you need to have stitches. It's the same sort of analogy that you would give with radiation toxicity or radiation healing. There's a certain dose at which your body will be able to heal, and that's really the job of the radiation oncologist to really like a skilled technician paint the dosage just so to allow your

body to heal while the cancer gets cured.

Darryl Mitteldorf: So there are people who are watching this who have gone through radiation therapy perhaps years ago and are thinking to themselves, "But I have a second cancer now. Didn't my radiation therapy cause that?"

Seth Blacksburg: Sure. It's a great question. So there's a whole field devoted to what's called secondary malignancy, so people essentially looking at data and saying, "What's the chance that somebody who was exposed to radiation now has a subsequent cancer later on in their life?" The chance of that is a statistical one, meaning there's no large study out there where people are followed for hundreds of months. What people have done is they've looked at young women who had breast cancer in the 1960s and had these large fields of radiation that were delivered back then, these are called mantel fields, and then they looked at them later on and said, "What was the chance of them developing breast cancer?" And there are large data bases where you can start measuring these. In general the dose of a radiation induced secondary cancer is extraordinary low. And it usually takes 20 years, 15 years, maybe 10 years at the earliest to even see. So when I council men on the rate of a radiation induced malignancy I'll tell them one out of 10 thousand, one out of 100 thousand, such that the risk of having prostate cancer, it's the number one cause of cancer in men, I'll tell that men, "Well, colorectal cancer is the number three cause of cancer in men. Bladder cancer is number four." Just because you have one cancer doesn't mean you can't have a subsequent cancer.

I will tell you, I am very thorough when I treat patients. I get images of them before I ever treat them. I want to have a good idea of what their prostate looks like and what the cancer itself looks like. And there are not insignificant amount of times I find incidental other malignancies. So to your question, if those men had been treated in 1980s before we ever had this sophistication of the images that man would have developed symptoms and someone could have easily said it was the radiation that caused that secondary cancer, whereas now I'm telling you incidentally any oncologist, whether a surgeon, radiation, or medical oncologist we see incidental secondary cancers all the time.

Darryl Mitteldorf: And I can tell you from the last three or four years we have a number of guys, not necessarily in our New York group, but in some of our groups int he Midwest that the group leaders there for Malecare have reported back bladder cancers are discovered as a consequence of prostate cancer and for those guys bladder cancer was the more acute issue. At least for those particular profiles of those particular guys. The idea though that it's not just the therapy, patients also have to go through CAT scans, they have to go through bone scans, a lot of radiological and radiation inducing scanning and things.

Seth Blacksburg: Sure.

Darryl Mitteldorf: All that combined, wouldn't that in itself ... I guess the better question is does radiation provoke a new cancer?

Seth Blacksburg: Radiation delivered to hundreds of millions of people will cause cancer in a very low number of people. So, with that said, when you have a child you try not to expose them to radiation. When you have any human being, you don't expose them to even a drop of radiation if they don't need it. Once someone has a diagnosis of cancer you're trying to cure them of their disease, prevent metastatic disease, let them live the rest of their lives. For that individual not exposing them to the necessary tests to accurately know where their tumor is essentially is much worse than the microscopic, minute chance that you may induce a secondary malignancy 20 years later. So really the issue at play, and we see really smart people who ask very thoughtful questions like this, is what's dangerous to an individual versus what is dangerous to a population? Exposing a population, hundreds of millions of people, to radiation needlessly will cause cancer in a very small number of people. For people who already have that diagnosis to better assess what the cancer status is you have to expose them, but the exposure they're getting is such a trivial thing it's not something that we really ... It's something I talk to patients about, clearly, but it's not something I would ever avoid.

Darryl Mitteldorf: Is there a number of CAT scans that you could tell us would be the upper limit of a normal human being to have?

Seth Blacksburg: So these are things that people do study. They're usually radiation biologists. And part of the reason I can't give you specific number of CAT scans is because the dose of radiation that's being delivered by CAT scans keeps getting less and less. So as our technology gets better we're able to do very low dose radiation imaging. But that'd be very appropriate for a radiologist, people who utilize these tests. It's something that gets measured, but again, its a concept that I often feel that very smart people, very smart people, often it's challenging for them sometimes to navigate because the issue at play is not, "Do I want to take a group of ten year olds and start getting CAT scans of their heads for fun and expose them needlessly to radiation?" The issue at hand is, "I know somebody has a cancer. I really have to know what the status of that cancer is and I need to aim some therapy, whether it's surgery, radiation, or chemotherapy." And in that context, when I say necessary evil I think even the word evil would imply the negatives are that high. It's something that is measurable in only calculated methods. The number of people who end up having secondary malignancies from radiation is extraordinarily low.

Darryl Mitteldorf: Not to grind this into the ground, but prostate cancer guys typically 50, 60, 70 years old they're also dealing with cardiac surveillance, so they have radiological dyes.

Seth Blacksburg: They take airplanes, they're exposed to radiation by being in the air. You and I are exposed to radiation by walking outside where ionizing radiation from the sun.

Darryl Mitteldorf: Which raises, should people fly less? We should live our lives and be happy, but it's only been in the last two or three decades that people have had these extraordinary environmental exposures that probably are benign. I'm on the same page with you, better to find out and it's useful and all that, but there are people watching this and I sort of bought into this years ago that what if? Maybe I shouldn't fly three times a week or something.

Seth Blacksburg: Well, somebody can turn around and say you're exposed to radiation in other ways. Not to drive you mad, but eat a banana, there's some trace amounts of radioactivity in the potassium. We are surrounded by a world that has radiation. Most of it is not ionizing, which is capable of damaging normal cells, but a lot of it is. I think the guiding principle, the northern star so to speak that most people who administer a test or a therapy, they'll use a concept called ALARA, so as low as reasonably attainable or achievable. So you really want to be judicious with doing it. Nobody ever orders a scan lightly, or they shouldn't. Nobody ever gives treatment lightly, or they shouldn't. But in every single case when you're doing it you're doing it for a good reason and the damage that you would be causing is so far outweighed by the benefit you're providing. It goes into the category, usually, of something that doesn't even truly get discussed often.

Darryl Mitteldorf: You need information, you need understanding before you make a treatment choice.

Seth Blacksburg: Sure.

Darryl Mitteldorf: And diagnostic tools like scans are one of the ways to find that information.

Seth Blacksburg: It's essential. So let's talk about the case of a really smart person who I see who says to me, "I will not cat a CAT scan." So that person is putting their life in jeopardy. So think about the irony, for the one in X million chance that the CAT scan would expose me to a cancer 20 years from now I will not have the therapy to cure me of the disease I already know I have. It's a little bit of a psychological problem when you're dealing with a reasonable person. Most people would, I think, make a decision based on health and reason [inaudible 00:15:52].

Darryl Mitteldorf: You use the term radiologist, radiation oncologist, there are also medical physicists and stuff. What are all these people?

Seth Blacksburg: That's a good question. If you asked my mother what I do for a living my mother will tell you I'm a radiologist oncologist. Radiation oncology has nothing to do with radiology. So it's a way of thinking, it's like your orthopedic surgeon has nothing to do with being an orthodontist. They sound similar, nothing related. So a radiation oncologist is a cancer doctor who studies how to deliver radiation to cure cancer. So that's really what a radiation oncologist is. There are other ways of curing cancer. You can cure cancer with chemotherapy, so that's a medical oncologist. And you can cure cancer with surgery, so that's a surgical oncologist. And those are the three types of oncologists who are out there. In order to use radiation we work with superstars, we work with PHD and master level medical physicists, people who have exquisite training, they're able to help us with the machines, they're able to help us develop the plans. I will tell you I married a medical physicist, so we talk shop quite a bit. But they're very smart people who, it's unique, but they work in the field of radiation oncologist.

Darryl Mitteldorf: Let's get into a bit of what you actually do. Let's transition too by me asking you

what's new and great in radiation therapy?

Seth Blacksburg: That's a great question. What's new and great is as our precision is getting better and better, so the machines like the Cyberknife, the unit that we have, we're able to test the doses a little bit better. We're able to raise the doses a little bit, we're able to study the interaction with other substances. So can you give radiation with other agents that may make radiation more effective? Can you treat different areas? Can you take people who have metastatic disease and essentially let them die not from their cancer? All that is fascinating, and it's really, for people like me, it's a page turner and it's something that we read about in every single month every new journal.

Darryl Mitteldorf: Mm-hmm (affirmative), good. So I have hundreds if not 38 questions that people have emailed in, so well get into that a bit. Actually, would you mind sitting a little closer so people get both of your shoulders I guess? This is Seth Blacksburg, doctor of radiation oncology. Why don't you tell us all in five minutes or less, or three minutes or less, what is Cyberknife? What is that about?

Seth Blacksburg: So let me give it, I'll characterize radiation in general. So in general radiation's delivered through radioactive material like seeds. So seed implants, radioactive catheters, or on these large machines called linear accelerators. The old way of delivering radiation with these linear accelerators is you would have a beam go through one side of the body and it comes out the other side. The beam goes in through another side of the body, it goes out through the other side. Starting in the 1990s you had a technology that really was all computerized which was called IMRT, intensely modulated radiation. All that means it's modern day radiation that's fueled by computers, where the beams of radiation don't just go into you and out you with just very few beams, you can generate hundreds of beams, seven beams, as many as you want to really shape the radiation very precisely. The Cyberknife is sort of the end of that evolutionary tree. It's a radiation machine that's been miniaturized and it's been put on a robotic arm. So with that radiation it's able to do two things extraordinarily uniquely.

One of the advantages is since it's on a robotic arm the beams of radiation don't move like a record player in an arch trajectory around the body. Instead, on a robotic arm you come from hundreds of different angles. An infinite number of angles and directions you can aim the radiation. As a result of that, that's called noncoplaner treatment, you can dial the radiation to a much tighter area. So much more precisely delivered. The parts at the edge of that area still see high dose, but as you move away from that little cocoon, that little shell of radiation that's being delivered wherever you're delivering it to in the body the dose falls off rapidly. So it's a major innovation and you're really exposing a lower volume of normal tissue to the treatment.

Darryl Mitteldorf: So I hear two things. One, the robot part of it. The miniature linear accelerator, and linear accelerator-

Seth Blacksburg: That's just the machine. Linear accelerator is what delivers the radiation.

Darryl Mitteldorf: Okay. And linear acceleration is just you're accelerating-

Seth Blacksburg: It gets into the physics of how it works. You're accelerating an electron that will essentially will generate a high energy x-ray.

Darryl Mitteldorf: Okay. So the robotic arm versus the external beam that many people are familiar. The external beam thing moves around.

Seth Blacksburg: It has a fixed arm called a gantry. It's a large machine with this fixed arm, it can only spin around like a record player.

Darryl Mitteldorf: Okay. So the robotic arm that you're talking about, and I wish we had pictures or a model. I wish we had an operating model of this. A Lego.

Seth Blacksburg: Sure. Well think about your hand and your arm.

Darryl Mitteldorf: Right.

Seth Blacksburg: Think about if you're able to move-

Darryl Mitteldorf: Here, I'm the prostate.

Seth Blacksburg: If you're able to bend your elbow and flex your wrist and move your fingers that's what the machine's able to do. It's bale to come in whatever direction it needs to.

Darryl Mitteldorf: Think of what films that we've seen of Ford, or Toyota, or car manufacturers. The robots that pain those cars.

Seth Blacksburg: That's right. And that is the robot, it's the KUKA robot. That is the robot.

Darryl Mitteldorf: That sounds almost like, "My God, I'm going to be treated by a car or by Toyota?" But think of this. My friends, think of this. This robot, how do you pronounce, KUKA?

Seth Blacksburg: It's the KUKA robot.

Darryl Mitteldorf: KUKA, yeah. That's been around for at least 25 years.

Seth Blacksburg: Sure.

Darryl Mitteldorf: And it's been perfected and gone through an insane number of versions, and the software that controls it has been refined and refined. That thing is the most accurate deliverer of paint or anything like paint on the planet, and every five minutes it gets better because it's in the interest of the manufacturer to please Toyota, and Ford, and all the other car manufacturers and all the other of their customers to make it better, and better, and better. The competition is nicking at their heels. But this is a brilliant device, and to use it for delivering radiation

therapy is just what a marvel. Whoever thought to-

Seth Blacksburg: So it was a neurosurgeon at Stanford University named John Adler, and he trained with a famous neurosurgeon from Scandinavia who had developed a machine called a Gammaknife, where you put people in this metal halo that had radioactive ports in it and they could very precisely treat an area. This neurosurgeon was a brilliant gentleman who developed a concept and said, "The radiation oncologists are doing it all wrong, I found a better way of using the Gammaknife. And instead of screwing people's skulls into this rigid body and having naturally radioactive materials that are placed into the ports, instead I don't need to screw somebody's skull into a frame, I'm able to develop a machine that will watch as the skull's moving and it can deliver radiation on the robotic platform." And that was the innovation.

Darryl Mitteldorf: It's brilliant. So there are two aspects of this that really just jazz me up is the idea of precision and of dosing. Let's talk about precision a bit.

Seth Blacksburg: Sure.

Darryl Mitteldorf: A person sits on a bed in the radiation theater, or what do you call the room?

Seth Blacksburg: The vault.

Darryl Mitteldorf: The vault? Oh, that's-

Seth Blacksburg: It's technically a vault. It's lead lined walls, but it's just the room. You don't even know it's a vault.

Darryl Mitteldorf: Okay, it's just a room. So there's lead on the floors as well?

Seth Blacksburg: Yes. There's lead all around just to prevent any leakage of radiation.

Darryl Mitteldorf: So Superman would be okay I guess? Or I don't know if lead prevents kryptonite.

Seth Blacksburg: Yeah, there's no kryptonite.

Darryl Mitteldorf: So the idea of, okay, so you're laying down, but you're breathing, your body's moving, how does the machine ... I know the answer to this, I want to ask the question in a clever way, but I'll just as it in a simple way. How does the machine track the prostate and make sure it doesn't hit on something else?

Seth Blacksburg: When I was talking about the Cyberknife I was saying there was two innovations. The first innovation is the noncoplaner, so the aspect of coming from so many different angles where you compact the dose of radiation very tightly. That's extraordinarily important when you're thinking about treating prostate cancer and you're trying to limit a dose to the testicles, or to the base of the penis, or to the bladder, to the rectum. Being able to pack that dose together is extremely important and we can measure very clearly the benefits of using that technology.

That's the mech. What we know is the mech doesn't always match the territory. So right now my heart is moving, and my liver is moving, and my lungs are moving. If you stapled me to the wall all those structures are still moving inside of my body. When prostate cancer has traditionally been treated, so when you talk about IMRT or the computerized radiation, people are laying down. The machine is able to see the target before treatment, but not during treatment.

The other innovation of the Cyberknife is it's watching the target as it's moving. So every 30 or 60 seconds it's taking what's called orthogonal parallel voltage x-rays. It's taking very low radiation x-rays at an angle to one another and it's watching little gold markers that have been implanted into the prostate move. And it's able to watch the prostate move in six degrees of rotation. So you're watching X, Y, Z, and roll, pitch, yaw. So really every single aspect, every plane of a prostate or a target's motion you're able to take account for. And not just for the treatment, but during the entirety of the treatment. And that precision, again, it's about half a millimeter. So less than a strand of hair.

Darryl Mitteldorf: So let's just back track a tiny bit. Gold markers, what does that involve for the patient?

Seth Blacksburg: So in order to ... When we're treating different areas of the body there are different requirements on the Cyberknife machine. So if we're treating a lesion in the brain for instance we don't need to guide the target because the brain doesn't move independent of the skull. So if you start holding me in a normal position and you're watching my skull move my brain's not moving independent of that. We'll make a little mold of somebody's pelvis, but they're laying freely on what we call a couch. It's not very comfortable, it's a hard surface. And they're in a larger room, there's no claustrophobia, it's not like being in an MRI or anything like that, and this machine is moving around them. It doesn't know what a prostate looks like, so it watches your pelvis but your prostate's moving sometimes independent of your pelvis. In order to harness the power of the machine for your prostate we'll put little pieces of gold in the prostate. They're a few millimeters, they're little pieces that stay in you for life. They don't cause any issues.

The analogy I'll give to the guys we treat, think about having dental work done. You have a cavity filled, you don't know it's there. If somebody did an x-ray of your mouth they may be able to see some of the scatter x-rays of that, but you don't even know it's there. In order to put it there we have a procedure where we will place the little gold markers usually with a needle into the prostate. It's a one time procedure, they stay in guys for life, and that's the process of putting the gold markers in.

Darryl Mitteldorf: So the gold markers, again, not to get too deep in the woods here, but there are two different kinds. One that looks like a grain of rice, or it's described that way, and there's another kind called an anchor that's weird looking?

Seth Blacksburg: That's good that you know. There are actually quite a few. There are quite a few, and just like Coke and Pepsi think they have the special sauce and everybody's got

their own opinion really the Cyberknife ... When you treat with the bread and butter IMRT machine it's sometimes helpful to still have gold markers, but the machines don't have requirements because it's still a human being on the other side who's lining things up and pressing the button. The Cyberknife still have human beings, highly skilled therapists, who are there, but the machine, since it's automatically taking into account motion, has a lot of requirements on how we place those gold markers. So we spend a lot of time on it, we actually conduct a lot of research on it. There are a lot of different markers that one can use. We have our manufacturer that we prefer to use, but if you go to Cyberknife centers anywhere in the country they're gonna use their own manufacturers and that's all fine as long as they're placing them in a certain manner that it needs to be done in.

Darryl Mitteldorf: So it's not like really a patient choice or-

Seth Blacksburg: To have the gold markers?

Darryl Mitteldorf: No, no, particular kind or-

Seth Blacksburg: No. I joke around with guys, I say, "We're gonna make your prostate worth a little bit more money today." Some kind of schlaky humor like that. But they're very tiny.

Darryl Mitteldorf: How much are they? How much more is the prostate?

Seth Blacksburg: Well, they're 14 karat gold and they're higher grade karat from what I'm told by the manufacturers than jewelry, but I don't know how much.

Darryl Mitteldorf: Think how romantic it would be to have your partner or child's name etched into one of those.

Seth Blacksburg: Sure. We don't put too many, we only put four in.

Darryl Mitteldorf: Okay, but there's a side business.

Seth Blacksburg: Sure.

Darryl Mitteldorf: Yeah. The idea that you're tracking the prostate, but you're also radiating the seminal vesicles, aren't you?

Seth Blacksburg: If that's part of the target. So you don't always have to target the seminal vesicles. In men that have low risk prostate cancer you really don't have to, the data's not compelling that there's an advantage. Usually when guys have a little bit more advanced cancer you are aiming at some of the seminal vesicles. Everybody's seminal vesicles, for guys who don't know, seminal vesicles are the drainage part of the prostate. Some seminal vesicles look like, remember Wilford Brimley? Big bushy mustache from Cocoon movie, or some look like Dali. Everybody's seminal vesicles look quite different, and usually when you're aiming at that part of the prostate they're just like the bunny ears on a rabbit. You're aiming at only one centimeter, 1.5 centimeter. You're aiming at a very small amount of them, you're

not chasing them all the way down with the radiation.

Darryl Mitteldorf: Okay. And lymph nodes? Do you go after those?

Seth Blacksburg: It really depends. So when I see guys, it's not cookie cutter medicine. We spend a lot of time, so I'll spend over usually about an hour or so with guys when I see them for a new diagnosis of prostate cancer. We'll go through all the tests that they've had and we'll explain to them what they're at a highest risk of the cancer spreading to, and based on the risk of cancer spread it would dictate what areas we need to treat. So if a guy has a very low risk of having prostate cancer that has spread in his pelvic lymph nodes I will not direct any radiation to his pelvic lymph nodes. If I a guy has very aggressive disease where I know he has cancer in the lymph nodes, or he just has such aggressive disease that the probability is so exquisitely high we will give him radiation to the lymph nodes. That's one of the advantages of the treatment we can give.

Darryl Mitteldorf: Now African-American men present at a higher rate of advanced stage disease. African-American men die at over two times the rate of Caucasian men from prostate cancer. Do you put a heightened regency or something on the African-American patients that you see around staging?

Seth Blacksburg: Do I council them differently?

Darryl Mitteldorf: Yeah.

Seth Blacksburg: So I look at risk factors for people who might have a more aggressive variant. I don't deny ... It's a question that gets asked, should African-American men not have active surveillance as one of the options? So you see a gentleman who's African-American, he has Gleason six, not aggressive. He has cancer you can't feel on a physical exam. He has a PSA that's very low, plus or minus any of these other tests. Is it wrong to offer that man active surveillance based on the preponderance of data that we have and people really studying it? It's not wrong. You can offer that man active surveillance such that it's active. There are a lot of thoughts on why African-American men have higher rates of prostate cancer, nobody knows. And a lot of people have looked at this, so they've asked is there something genetically different? So maybe there's something genetically different about African-American prostate, the gentleman's prostate cancer, and that's why it's more advanced by the time it's discovered. There's a question of socioeconomic factors. So perhaps those are gentlemen who don't get screened as often by PSA tests.

There's a question I find very interesting, perhaps men of different ethnicities the cancer can be located in different areas. So there's one theory that African-American men, their cancers may be more higher up in the prostate where biopsies may not touch that cancer where they never were diagnosed. These are all competing theories, nobody has the answer, but obviously it gets played into that whole Rue Goldberg thought process of how to council somebody appropriately.

Darryl Mitteldorf: Let's now talk about the advance around the dosing. To my mind the question

really is external beam radiation, you show up for 35 to 40 times, five times a week, six to eight weeks. Cyberknife is just five times. Tell me about this.

Seth Blacksburg: So with conventional radiation, remember what I mentioned one of the weaknesses is that you have a target that's moving but you don't see it move during the treatment. So with conventional radiation the design is that you're going to treat a broader area where more of the bladder and more of the rectum is in that area. And one of the first things we talked about was how do you preferentially damage cancer and not normal tissue, and one of the ways you do that is it's a concept from the 1960s, it's called fractionation. So divide your radiation into tiny little pieces to let your body heal in between each fraction. So that concept is a very old one and it's in the field of radiation biology. The question is what if you now have precision? Now you're not in the black box in an area, but you see the target and you see it dynamically as it's moving through every single plane. So you're gonna treat some bladder and rectum, but a much, much smaller volume. Can you up the dose a little bit?

So prostate cancer has a unique biology where it's more sensitive when you give it larger doses of treatment. That's a little bit unique in the word of cancer. So with the technology and that radiobiology aspect, if you give a prostate cancer a lot of dose you actually can have a much more effective treatment. So couples with the technology you are able to give five treatments with a higher dose per treatment, and you're actually giving the gentleman's cancer a much higher dose and you're giving the normal tissue a much lower dose. There's a whole algorithm on that, it's called biologic effective dose. If you look online at BED, or biologic effective dose, it's gonna go into a lot of radiation biology and concepts called alpha and beta and ratios where people have spent entire careers on this, but suffice to say the data's pretty compelling and you now have data that goes out well over a decade showing how effective it is when you're giving higher doses per treatment.

Darryl Mitteldorf: So patients were told 15 years ago that you're gonna have 40 doses because each day your body will have an incremental effect that the next day's dose will work on, and work on, and work on. You're saying now that we know differently? That a larger dose five times within a week is actually more effective long term?

Seth Blacksburg: So it's not the concept of the cancer so much as the normal tissue. So the reason that radiation historically has been fractionated is the concept of repair, let your normal tissue repair itself between each treatment. It was always known that prostate cancer had this lower alpha/beta ratio and people would theorize and say, "Perhaps if I had the technology to more precisely deliver that large dose it will be effective." And in fact 30 years ago people were doing what's called high dose brachytherapy where they were putting catheters inside of people and delivering this same dosage that we're actually delivering today, but without radioactive material inserting.

Darryl Mitteldorf: One of Malecare's early supporters, Andy Grove from Intel Corporation had high dose brachytherapy.

Seth Blacksburg: Sure. So the dosage that are now being harnessed on a robotic machine, the dose is the dose as my partner John Hoss always says. And I like that expression because it's true, the Cyberknife doses that we're giving, it's not new. They've been around for decades, they've been around for 30 years the same way Da Vinci robotic surgery, that's only been prime time for 12 years but the concept of the prostatectomy has been around since 1978. So you're just extrapolating on something that didn't have the same technologic advantage years ago.

Darryl Mitteldorf: It's also different in the sense, the Da Vinci surgery isn't having an added value around how it's removing the prostate, it's just a different way to remove it.

Seth Blacksburg: Well, a robotic surgeon would probably disagree with you. I'm not a robotic surgeon, but a robotic surgeon would say, "You have much shorter recovery time. I'm cutting less tissue."

Darryl Mitteldorf: But in terms of the effectiveness. The prostate's out whether you had it done ... However you pull it out, it's out. With dose delivery, understanding the higher quality and a more precise way of doing dose delivery and doing it in a higher rate within a shorter period of time you have a different kind of long term effect than you would at the 40 fractions.

Seth Blacksburg: Yes.

Darryl Mitteldorf: And that's an added value that the precision of using a robotic arm offers the patient. And that to me is exciting.

Seth Blacksburg: It's very exciting, absolutely. It's why I spend all my time working on counseling patients on studying.

Darryl Mitteldorf: I don't, but it's still exciting.

Seth Blacksburg: It is, it's amazing.

Darryl Mitteldorf: The idea that it's five times, so if five times is an advantage why not three times?

Seth Blacksburg: That's a great question. Remember when you asked me what's in the forefront, what are people looking at? People are mixing up the fractionations, but they're studying it. Nobody wants to be the guinea pig. We know it's safe to give this dose. In our own institution we've treated more than any place in the country. We treated over 4000 men with this type of treatment, and we know it's safe because we follow men. We have our own database. Other institutions internationally have used doses like this. There are people who are now building protocols, and that's what's exciting. Can we do it in four doses? Three doses? One dose, two dose? It's all about finding out how to optimally treat the cancer, cure people, and minimize long term side effects.

A lot of the concept of ... So we talked about the classical way with radiation is this long protracted course of treatment. So usually with prostate cancer for instance

it's nine weeks, 45 treatments or whatever. Breast cancer traditionally it's this long course also. A lot of the changes in that conception had to do with access to care, so it had to do with folks in England and in Canada who had very sophisticated radiation units but nowhere near what they had in the States saying, "You know what? In the interest of cost effective medicine and access to care, can we get equivalent outcomes by truncating this treatment just a little bit? Especially as the technology gets better let's keep truncating it a little bit more and more." That's called hypofractionation and it's very much prime time, it's a standard of care, and really the impetuous behind it was simply access to care. If you take that spectrum as you were saying and you move it further and further there are places obviously where you don't have the ability to have a radiation center every other block and have all the sophisticated technology, and there's a true advantage to being able to treat people who are traveling distances, have poor access to care with larger doses per treatment if it can be safely done.

Darryl Mitteldorf: Sure, absolutely. When you do surgery you pull out the prostate, presumably some of it's now METs or it's gone to lymph or whatever you've got everything.

Seth Blacksburg: Presumably.

Darryl Mitteldorf: Presumably. And presumably [inaudible 00:42:21] or whatever. With radiation, with Cyberknife, can you reasonably within the high 90s tell a patient I killed every one of your cancer cells?

Seth Blacksburg: Yes. So the issue at play is that there's a psychological thing that men go through when they have cancer. It's not unique to men, women have it too. Anybody where I have it, I got to get it out. So there are men who they are exasperated when they have surgery and the cancer comes back. And that concept, how did the cancer come back, it's lost on them a little bit sometimes. So the issue is there's the cancer we know about and the cancer we don't know about. So we have amazing technology in the year 2018. You have very sophisticated MRIs, you have really good CAT scans, really good ultrasounds, biopsies are getting better, genetic tests. You have all this information, I say the three blind men and the elephant, we're really able to see what that elephant looks like much better each year. The issue at play is there's always the chance that there can be microscopic disease we do not know about. So the advantage of surgery, so I never bash surgery, I work with the surgeons with whom I collaborate, I don't try to compete with them. So I think surgery's an amazing treatment and it's got some advantages.

With surgery you're cutting through the base of the bladder, you're cutting through the urethra, the tube that connects the bladder to the end of the penis, you're taking the prostate out and reattaching things. So the benefits of surgery is any disease that is housed in the prostate you are removing it. So you're not relying on that cancer to die off, you're simply taking it out. So that's why if a guy has low risk prostate cancer his chance of cure is very high, and if a guy has aggressive prostate cancer his chances are gonna be lower. The issue at play is there could be microscopic disease that's just outside the prostate, microscopic disease that went into the seminal vesicles, microscopic disease that could be in the lymph nodes,

wherever it is. With radiation the relative value is you're treating a small cocoon of energy that surrounds the prostate. So the competitive advantage of surgery is I'm removing your entire prostate with the cancer in it. The competitive advantage of radiation is the cancer inside is dying off, but I'm also providing a cocoon of a few millimeters outside of that are where if you do have a risk of extracapsular disease, microscopic disease that no MRI, CAT scan, PET scan, bone scan could ever see you're actually accounting for that.

And in fact, I was in Forbes magazine arguing with a surgeon over saying, "Let's spar over the low risk guys. If we were to compete, let's have a friendly discourse over low risk patients competing against killing off the cancer or removing it all. Let's not compete with the high risk guys." Because in my opinion, radiation has a clear advantage in those cases. The clear advantage is you're bathing tissues that have a high risk of microscopic disease where a surgeon, it's not like the liver, you were mentioning a liver study. the liver's a huge organ. You could cut very wide margins around a tumor so if there's microscopic disease you can account for it, but the prostate, it's connected to the bladder. The rectum's right there, the nerves that control erections are on the sides. You can't cut a huge swath of normal tissue around. There's a little bit of an unfair advantage that radiation has over surgery, and I'm very candid with patients about that. And the unfair advantage is with surgery usually you know the erections have gone down because the mechanism is you cut the nerves that control erections, it's like cutting the wires in the ceiling, light goes out. Sometimes guys will get a little benefit over time, but usually you know pretty early on that there's been damage that's been born.

The unfair advantage radiation has, and it is unfair from a purist standpoint but it is what it is, is often time it takes time to watch erections go down after radiation. So what's unfair about that is think about every single man or woman who's watching this right now, or thinking about this. If that guy graded or his significant other graded that man's erections compared to what they used to be five years ago, ten years ago, as we get older there's a natural process of decline in erectile function. For most guys. And so sometimes it's hard to tease out that data, but we have data. So when I see men I will council them on the rate of erectile dysfunction. I'll tell them what we try to do differently to limit that disfunction. And again, it's not cookie cutter, but we really customize quite a bit the care to try to minimize that.

Darryl Mitteldorf: Right. And the idea of length and shrinkage, that's usually a question.

Seth Blacksburg: Of the penis?

Darryl Mitteldorf: Yeah. Surgery patients, almost nine out of ten surgery patients will bring that up in a support group setting. "I used to have a giant and now I'm a dwarf." Or whatever. Does radiation impact length?

Seth Blacksburg: No. So radiation does not. If you utilize something called hormone therapy, which is essentially chemically castrating somebody for a period of time, that may decrease sometimes length of the penis, but in general the radiation does not affect penis size.

Darryl Mitteldorf: In 60 seconds or less, what is it about radiation that impacts erectile function?

Seth Blacksburg: There's actually debates on that so there are probably three different ways that people theorize that erections can get damaged over time by radiation and it's why people like myself and physicians who are paying a lot of attention in designing radiation they try to limit dose to these areas. One is to the blood vessels. Why do men have decreased erections over time just as we get older? Some of it is that nerves don't work as well, some is that you get hardening of the arteries. So a lot of people with diabetes have worse erections, or people with blood pressure issues. So one of the areas could be blood vessels. One of the areas could be just the neurovascular bundles themselves. So we know that's the mechanism with surgery, so if a surgeon cuts through those nerves that's it. The erection's gonna go. That said, even when a surgeon spares the nerves erections go down, so there may be another mechanism of that happening.

The last, which is classically thought of in the world of radiation is that there may be some dose to the base of the penis called the penile bulb. So for instance, people like me when we study, remember I mentioned the first advantage of the Cyberknife was the noncoplaner aspect? The beams coming from all over, the dose getting served with a tighter shell? When I look at the penile bulb doses of the men I'm treating it is an order of magnitude lower than when I used to use IMRT. So that is demonstrable, and it's because the doses are getting packed together. Can I prove that that's the reason why the erectile function tends to be very good in the guys we treat? I can't. And all treatment has a chance of erections going down, so I never sugar coat that for guys. I'll always tell them. If you see a doctor who tells you erections don't go down, or not in my hands, or I can give a cadaver an erection, or any of these sort of expressions you should run, it's not an honest doctor. But we can quantify to what degree erections go down.

Darryl Mitteldorf: And when you say a doctor says erections won't go down in my hands, of course that does another thing. So the idea of ejaculate, that's gone with radiation?

Seth Blacksburg: That should be gone for the most part. So with surgery you're really not gonna have any ejaculate. With radiation the vast majority of the ejaculate goes down. I do see guys who say, "Well, I have a little ejaculate." You have other structures in that area, but in general your ejaculate does go down.

Darryl Mitteldorf: So sperm banking before radiation therapy?

Seth Blacksburg: I think it's important. I ask guys, and I use the word, "I've been humbled." I've been humbled not just with cancer outcomes and in general, but also everybody has their own preference. I saw a gentleman in his late 70s the other day who wants to bank his sperm, so I actually ask every one of my patients, "Are you planning on having children at some point?" What's interesting is that the radiation does not affect the testicles. So again, that benefit of the Cyberknife, I'm in the process of writing a manuscript and I've presented this at a national meeting, the dose we give to the testicles, which present sperm, is actually lower with this treatment

than any other form of radiation. So you still make sperm, but the ejaculate, which is the transit system for the sperm, that will go down. It's more challenging to have children. There are guys I've treated who have said, "I get it, I'm whatever." And they've impregnated their significant other. So it can happen, just the chance of that is very low.

Darryl Mitteldorf: Okay.

Seth Blacksburg: If you look at the data that's been published there are rates that go out there with incontinence with surgery. There's a large study that was published in the New England Journal of Medicine called the Pivot trail where men had 15-20% rates of needing pads, or diapers, or having that leakage. With modern day surgery it could be lower than that, but that's sort of incontinence in general. With radiation, whether Cyberknife or any of the other types, there's always a chance of that but it's very low. So if I see guys and they say, "What's the rate I'm going to have incontinence?" I say, "The way that you're thinking, the stress incontinence where you lift something heavy, you cough or sneeze and it comes out, you can't control it, that's gonna be less than 1% for most guys."

What radiation does cause is irritation, so men will urinate more frequently and more urgently. Guys don't think of that as incontinence, but there's a medical term called urge incontinence, which means I control my urine, I do not wear diapers, I don't wear pads, but if I have to pee and I'm not near a restroom I might have an accident. And certainly with radiation that's something that can happen to guys, and that's part of what people like me do for a living, we don't just try to treat guys and cure them of the cancer, we try to handle side effects. We'll put guys on anti inflammatories, or Flomex, or other medications.

Darryl Mitteldorf: How long are they on the table?

Seth Blacksburg: So with the newer version of the Cyberknife usually it's about a 20 minute treatment. Sometimes it's quicker, so I've treated guys in 14 minutes, I've treated guys where it takes longer, 25 minutes. On this newer version of the Cyberknife, which we have, it's I'd say on average about 20 minutes.

Darryl Mitteldorf: And are you physically there?

Seth Blacksburg: I am. So I'm pretty anal, as you might be able to tell, so I'm there for every single treatment. I will tell you I'm part of the advisory board on the company that makes the Cyberknife and I go to these meetings. There's a wide variation on how often physicians are physically present and watching. The vast majority of physicians are there or should be there. We have therapists, so the machine's doing most of the heavy lifting. The machine has the ability to watch and to move dynamically. We have amazing radiation therapists who are there on the machine and watching and calibrating. I always check on a daily basis all the treatments.

Darryl Mitteldorf: Okay. And the treatment, it's not like you're sitting there with a joy stick zapping. It's already preprogrammed.

Seth Blacksburg: It's preprogrammed. So as I mentioned, we have PHD level and masters level physicists. We have dose symmetrists, which is a whole other field. We have people who put together the radiation plans, people like me, the doctors review them. Sometimes it's iterative where I'll say, "Get the dose down lower here." Or, "I like it." Or, "Improve the dose here." It's a process, we review it. There's a lot of sophistication in that, and then once the plan is ready and we think it's good it goes to the machine and the machine will deliver what we plan. That's what I meant by ... In my opinion one of the benefits of the Cyberknife is the map matches the territory. So I plan something and I have very high confidence that what we plan gets delivered, whereas with other machines you could have a really good map but that's not always what gets delivered because it's not watching the prostate during the treatment.

The scenario that I would imagine that you were gonna go from here is what do you do when it's ... A lot of time, it's been three years, PSA's going up. The classical way of looking at this was cancer treatment didn't work, that's it. And so guys will go on hormone therapy, and there's different ways of doing that. I think though the correct way of handling that in the year 2018 is finding out where the cancer is. Where it is determines what I'm gonna do. So what surgeons sometimes will say to patients is, and there's some [inaudible 00:55:19] surgeons who I've hear say something like this is, "You should always do surgery, because if your surgery doesn't work we'll give you radiation afterwards. If your radiation doesn't work, can't do surgery." And I'll always tell patients that's only a half truth unfortunately.

The half truth aspect is if the surgery doesn't work my radiation field involves a lot of your bladder, so your side effects are gonna be much higher. Although you can be cured, and I treat guys all the time. The other half truth is it is harder to do surgery after radiation, but you can do cryotherapy. You can do high frequency ultrasound therapy. You could do radioactive seeds. You can mix some of them. You actually have more salvage options after radiation than if you had surgery. So the first thing is where's the cancer coming from? If the cancer is coming from some are in the prostate where it didn't die off then I will send a guy, when they're appropriately selected, for focal freezing, cryotherapy, focal high frequency ultrasounds, I'll send the guy for focal brachytherapy or radioactive seeds, and they're very high rates of salvage care.

if I find out that there's no cancer in the prostate, so we did the Cyberknife, guy has a rising PSA, but it's not from the prostate, it's that there was microscopic disease that probably always existed in the lymph nodes then I have to cross that bridge. And there are really high cure rates of high dose radiation to lymph nodes, or if you're worried about a region but you think the region in the lymph nodes, or even doing surgery, you start getting into an area where the data is a little bit all over the place and you really want smart people talking to each other. So usually in cases like those I'll present it at a tumor board or I'll speak to other doctors, we come to a consensus. It really depends on where the cancer is. If it's in one lymph nodes I'll use a Cyberknife, I'll blast that one lymph nodes. If it's in a number of lymph nodes then we're talking about conventional radiation or surgery.

Darryl Mitteldorf: Can you also do a palliative care for distant bone METs?

Seth Blacksburg: Absolutely. So the machine [shines 00:57:22], I've treated some very prominent individuals who are in the public life who you would never even know but they have metastatic prostate cancer. The cancer has spread where if it goes to the bone in the spine they may have some dysfunction and you could ablate that tumor and that guy can regain usage of his extremities or what have you. You can definitely treat it very well for this scenario.

Darryl Mitteldorf: Thank you. Dr. Blacksburg, thank you.

Seth Blacksburg: Thank you so much.

Darryl Mitteldorf: You've been exceedingly generous with your time and you knowledge.

Seth Blacksburg: My pleasure.

Darryl Mitteldorf: I hope it's been useful for our viewers.

Seth Blacksburg: Thank you.

Darryl Mitteldorf: Come and watch another show. Click subscribe, which I think is down there on YouTube. If not, you'll probably get an email for our next webcast. Thanks for watching, bye.