

Scott Redding:

Welcome to the 3Ps of Cancer podcast where we'll discuss prevention, preparedness, and progress in cancer treatments and research, brought to you by the University of Michigan Rogel Cancer Center. I'm Scott Redding.

Scott Redding:

We're here with Michigan medicine, Dr. John Krauss, medical director of the Multi-disciplinary Colorectal Cancer Clinic at the Rogel Cancer Center to talk about colorectal cancer and unresectable metastatic cancer treatments. Dr. Krauss has been practicing at Michigan medicine for the past 10 years. Prior, he was the associate director of the Ann Arbor Community Cancer Oncology Program at St. Joseph Mercy Hospital, and spent six years at the Cleveland Clinic.

Scott Redding:

He has a strong focus on therapeutic clinical trials, as well as programs to help improve communications with patients to make sure they are getting the best possible options for sustained quality of life, and optimum care for complex conditions. His main goal is improving the lives of cancer patients. Welcome John.

Dr. John Krauss:

Good morning, Scott.

Scott Redding:

We talk about colorectal cancer, but is there a difference between colon and rectal cancer, and is rectal cancer the same as anal cancer?

Dr. John Krauss:

So anal cancer is a totally separate cancer and has a totally different treatment, and surgery comes later. So everybody thinks about having their screening colonoscopy or some other tests to screen for colon cancer, and the rectum is the last part of the colon but there's no sharp dividing line that the person who's doing the colonoscopy can see where the rectum ends and where the colon starts. So colorectal cancer is lumped as kind of one big disease, but the management of rectal cancer, the management of the last part of the colon, is a lot different and requires really a multidisciplinary approach from the start.

Scott Redding:

You hear stories about people that get colonoscopy and a polyp is found while they're having that colonoscopy. And usually that can get taken care of at that time. Is that the same true, usually that's for colon cancer, is that the same true for rectal cancer? Or, if something gets noticed towards that bottom part where it would become as rectal cancer, is that treated much differently and a different approach?

Dr. John Krauss:

Let's just break it down to several different parts. So recent recommendations have been maybe the screening age for colonoscopies should be a little bit younger. The younger you go with screening age, so it had been 50, should it go down to 45? The younger you go more people will have normal colonoscopies. And there is some risk from a colonoscopy. The neat part about a colonoscopy, as you



mentioned, it's diagnostic. In other words, it finds polyps. And, it's therapeutic, it cuts polyps off. Now, polyps come in all shapes and sizes. Some of them are attached to a neat stalk and they just get snipped off and are easily retrieved. Some are like big flat quarters, or even silver dollars, stuck to the side of the colon. And if anybody's ever worked with sausage casing, you can see how thin an intestine lining is. And so cutting a silver dollar off the inside of a sausage, without poking a hole in the colon, is difficult.

Dr. John Krauss:

And some things are just obvious tumors to the person performing the colonoscopy. So if there's a tumor in there that's an inch or two inches or three inches big, that is pretty much going to be a tumor and it'll need to come out one way or the other. The endoscopist, the person, the gastroenterologist doing the procedure, usually knows roughly where they are. In other words, they can tell, oh, I'm in the first couple of inches, or I'm way at the other side of the colon.

Dr. John Krauss:

But that dividing line between that 15 to 20 centimeters in through colon, where the rectum ends and the sigmoid colon begins, is oftentimes not as clear. So most colonoscopies are going to be normal. You're just going to have a few polyps removed and they'll then send those polyps down to the lab. And if they come back totally benign they'll say, have a colonoscopy in three years, five years or 10 years, depending on your overall health status. Those ones that have more polyps will need to be checked a little bit more carefully. In other words, lesser interval to the next colonoscopy. And then those people that have cancer will need to have some type of therapy for that cancer.

Scott Redding:

Are there signs or symptoms to be aware of for rectal or colon cancer?

Dr. John Krauss:

We really want to catch it when it's not causing signs and symptoms. So the patients that are the sickest will just come in with symptoms of the disease that spread to their liver and their lungs. And that indicates generally a little bit more aggressive type of cancer. They might come in with jaundice or unexplained weight loss. Rectal bleeding is the most common sign of colon cancer. But it's very hard to distinguish rectal bleeding from a tumor from that from hemorrhoids, so hemorrhoidal bleeding is very common. But persistent rectal bleeding over a few days to a week probably should at least be investigated, but realizing that the vast majority of the time that will just be hemorrhoidal bleeding. And then certain times it's worthwhile to pursue it further with a test, a flexible sigmoidoscopy or colonoscopy, something like that.

Scott Redding:

So is the flexible sigmoidoscopy and the colonoscopy the best ways to detect rectal and colon cancer?

Dr. John Krauss:

So they're the most sensitive, but they're an invasive procedure. For the colonoscopy, the patient has to drink a prep which totally cleans out the colon, which is not very much fun. The flexible sigmoidoscopy that the lower part of the colon can just be cleaned out with an enema right before. Again, that makes us necessarily the most pleasant experience, but it's not drinking the one day or a two day prep. I'd say most providers are now going just straight to the colonoscopy. Flexible sigmoidoscopy can be done in an office a little bit quicker, but the better test will be the colonoscopy. Other screening tests include more



sensitive testing for blood that you can't see in the stool. And also then there's some DNA based tests where you actually provide a stool sample in a box to accompany, and they tell you the risk of colon cancer.

Scott Redding:

If we look at rectal cancer for a minute, and you talked about, there's a fine line between where the rectum and the-

Dr. John Krauss:

Large intestine. So the two anatomic parts are the descending colon. This is the part that comes down right to the sigmoid colon, than the sigmoid colon kind of sweeps around sigmoid for us, and then it goes into the rectum. So in the operating room, this is not a fine line. In other words, there's an obvious area. But from the endoscopist standpoint, they've got a snake basically with a light on the end, and they're looking up there and there's these three valves in the rectum, but then after that they go into the sigmoid colon. So sometimes they'll be in the sigmoid colon. Sometimes they'll be in the rectum. And the rectum's really pretty remarkable if you think about all the different things it has to do. So you're basically sitting on a valve, the valve has to be able to tell the difference between gas and liquid and solid.

Dr. John Krauss:

It has to be able to preferentially let out those things at different times. And then it has to store the fecal matter until you're ready to expel it. And so to store it expands. And sometimes you just think of it expanding like the balloon that somebody might tie into a dog for your kid. Just kind of going from a very tiny balloon to a very fat balloon. But it also expands going from a very short balloon to a very long balloon. And so that makes it even more tricky for the person putting the scope in you because sometimes that rectum, which would normally only be 10 centimeters, stretches out to 15 or 20 centimeters, just as kind of, well that's what the rectum does, it stores poop. And if you put a scope in, sometimes it just stretches out in front of the scope. And that's the kind of tricky part.

Dr. John Krauss:

So if you're dealing with what the endoscopist tells, you might be a sigmoid cancer or a rectal cancer, and this is just getting into the weeds in terms of the diagnosis. But in terms of, you kind of want to make sure is this a rectal cancer or not? And most people won't remember coming out of their colonoscopy, they've been sedated. But they should hand you a little picture of your colon and those cancers that are on the left side you want to talk to them maybe later on, or have your family member talk to them and say, is this a rectal cancer? Is this a sigmoid cancer? That's the key thing. Polyps doesn't matter so much, you just want to get rid of all the polyps.

Scott Redding:

So if we talk about the left side there, and you said that those are one that we want to maybe revisit with your doctor about. And we talk about rectal cancer and making sure it's rectal cancer, is there a particular reason why we'd want to make sure? Or is it treated different than a colon cancer would be treated?

Dr. John Krauss:



Correct. So that's the biggest reason. You're going to treat it ... The whole approach to treatment would be different. So a colon cancer that's right near the small intestine, called a right-sided colon cancer, can be treated with surgery. And typically this is a surgery performed by a skilled surgeon, of course, and they need to get the right number of lymph nodes out and perform a cancer operation. But this is a surgery that's much more straightforward and the anatomic boundaries are much more clearly defined. For a rectal cancer, the rectum lives for the most part down deep in the pelvis, and the anatomic boundaries are much harder to define for somebody who's not skilled in the art. And so the operation that's come to light over the last, basically generation, is something called a total mesorectal excision. Again, it's getting deep into the weeds, but a total mesorectal excision is the correct operation to perform for any cancers that hit that recto sigmoid junction, or dive down into the pelvis.

Dr. John Krauss:

And there's a lot of reasons for that. One, is to get good margins around the tumor. One, is to get all the lymph nodes out. And I've been in practice now for a number of years and it used to be they would just get down below the tumor and perform that anastomosis. Now, the colorectal board certified trained surgeons are doing this total mesorectal excision to get out sideways and to get those lymph nodes. More exciting than the operation, which is key, but hopefully you don't have to know about yourself, is that on a usual colon cancer that's not an emergency operation. You can just have the colon put back together and you don't have to have an ostomy. You might have to spend five to 10 days in the hospital, but then you go about your life and decide about whether you need further treatment or not.

Dr. John Krauss:

For a rectal cancer, if it's a very rectal cancer, you have this whole pelvic floor and the muscles that control your bowel movements. And so if it's too close to that pelvic floor, if it actually involves those muscles, then the patient's looking at potentially a permanent colostomy. And so that's obviously very intimidating for a lot of people. Most people don't know somebody with a permanent colostomy. So that's one of the reasons that people avoid screening is they don't even want to think about an ostomy. But then for rectal cancer treatment, we now, over the last 10 years to five years, have developed that some people can actually have techniques on which chemo and chemotherapy and radiation, and potentially avoid that operation, if their cancer goes away with the chemo radiation, and chemotherapy,

Scott Redding:

How do you decide which treatment course is best for a colon or rectal cancer patient?

Dr. John Krauss:

So the first part was that key part of defining it's a rectal cancer or a colon cancer. The next part is everybody should have a cat scan, or if they can't tolerate a cat scan an MRI to look for other spots of tumor. Most tumors, three quarters to 90% will not have other spots. And so there'll be a lower stage, not as stage four, being the highest stage. Even if it's stage four, we want to say, is it stage four with one or two tumors that we can potentially cut out? Or is it stage four with a hundred other tumors that we need to start with chemotherapy? So then if it's a rectal cancer, in addition to the cat scan, in addition to the routine blood work, addition to a general physical exam, to make sure the patient's healthy enough to receive the therapies, you want to get a rectal cancer protocol MRI.

Dr. John Krauss:



And this MRI is something that our radiologists here at Michigan medicine have just done a great job developing. CT scans are relatively simple to perform. There's not a lot of extra instruments set up between patients. MRIs are highly finely tuned. So even a good MRI machine can be off a little bit because they're running the liquid helium in this thing to get the magnet just the right way. And then we take it one extra step here. And once the patient with suspected rectal cancer, rectal sigmoid cancer, gets on the machine, the radiologist then sets up custom windows for that patient to make sure that they get what's called a cross sectional look. So that if you have a curve sausage, you don't want to be taking crust inside of that sausage. You want to make cross sectional lines across that sausage to tell the stage of the tumor.

Dr. John Krauss:

So each rectal cancer protocol MRI done here is custom protocol by the radiologist to get this perfect look. And even doing all that we then have a dedicated group of readers and we review all the rectal cancer, new rectal cancer diagnosis at our tumor board. And we all look at the pictures and say, "Oh yes, this is a less advanced T1 tumor. This is a more advanced T3 tumor that will then require all of our therapies." Chemotherapy, radiation therapy, and potentially surgery. So all of those things are key to good rectal cancer treatment. And once you have all of that decided then along with the patient, the medical oncologist, radiation oncologist, the surgeon, you chart a course. And so rectal cancer, the initial treatment courses takes a fair amount of testing.

Dr. John Krauss:

In addition, just having the surgeon, or having somebody that the surgeon trust, know exactly where that tumor is in the rectum. Is it relatively low down? It can be felt with just a regular rectal exam in the clinic. Is a little bit higher up, and the surgeon should do a flexible sigmoidoscopy to make sure that they've got in their mind what type of surgery they're going to have to do. So rectal cancer treatment is its own beast. And you want to make sure before you have a curative surgery that you have all this information. Do I have lymph nodes that are involved? Is the surgeon prepared to do a more extensive operation? Should the preoperative imaging be different than what they find in the operating room? And did I have the necessary chemotherapy radiation therapy to make sure I have the highest chance of cure going forward?

Scott Redding:

You've talked about a multidisciplinary team and looking at the tumors to figure out the best course of action. If we step away from the initial clinical side of things, what kind of research is happening around colon and rectal cancer?

Dr. John Krauss:

We participated with Memorial Sloan Kettering in 50 hospitals throughout the country for this rectal cancer organ preservation. So in other words, show that patients live just as long and not everybody needs an operation. So that's really been a pivotal trial that was presented by Dr. Aguilar at our annual meeting last year at the American Society of Clinical Oncology meeting. The radiation oncologist are working on better ways to target the radiation. This largely happens behind the scenes in terms of fancier machines that can have more customization in the fields, algorithms that will get better, dosing to the tumor and spare the normal tissues. In terms of trying to develop better therapeutics, that's a whole other realm. So over the last five years we've recognized that some tumors, a small percentage,



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maybe three to 5%, of colon and rectal tumors will respond to immunotherapy. And so we're trying to then take that into earlier stages.

Dr. John Krauss:

We know that some of them will respond dramatically with stage four cancer. Will the approved immunotherapies work better for stage two and three? And we recently completed accrual to a study with a national organization here, and the results were presented a couple of weeks ago. It showed no, immunotherapy does not add anything to standard chemo radiation. We have some other ideas of how to make it work better, but we have a lot more work to do. And then going forward, part of my work is helping get everybody on the same page and talking between the group of the best treatment for rectal cancer.

Dr. John Krauss:

But then ultimately some of those treatments will not be effective. Either the patient's cancer will be aggressive and show up at tumors in the liver or the lungs that can't be surgically removed, or they'll have initial treatment and it'll come back and won't be able to be cut out surgically resected. So then developing new therapeutics for colon and rectal cancer, trying new medications that treat the cancer at every site in the body to hopefully control it, shrink it down, put the people in a long term remission.

Scott Redding:

Can we go back to rectal preservation for a minute, if with this new research out and you said, it sounds like it's going to be very, very promising. Does this, maybe down the road, have a chance of replacing having a permanent ostomy? As you had mentioned earlier that that some rectal patients get.

Dr. John Krauss:

Right. So the results that were presented at the American Society of Clinical Oncology meeting, we weren't sure which was the better way to do this. Should we give the chemotherapy first, then the chemotherapy and radiation together? So it's a long course. It's four months of chemo then it's a 25 to 28 treatments of radiation. And then assess for the tumor going away completely. And the assessment has to be by looking inside with a sigmoidoscopy, looking from the outside with an MRI, and looking at the lungs and the liver with a cat scan. Or, should we do the chemo radiation first, then followed by the chemotherapy? And we showed that we were able to double the organ preservation rate. In other words, twice as many people went in if we did the chemo radiation first. And so we're looking for some tumors, maybe as many as 40 or 50% of the people will go into a complete remission after this close to eight month treatment.

Dr. John Krauss:

Now it's still relatively early days because, I'll say early, we've been doing it for eight years, but we want 20, 30 year survivals. And so yes, some of the people who go into complete remission will relapse and then have to have a surgery later on. But the survival is exactly the same in terms of whether we do surgery now or a little bit later. And some people just aren't comfortable with getting every three to six month MRIs, and getting every six month endoscopy's. They say, "No I know this cancer was there. It's just going to bother me psychologically, and I want to have it out." And that's a perfectly acceptable thing too. So there's, what we'll call, shared decision-making. Looking at the patient's values, looking at the patient's general medical condition. Some patients, those people over 80 to 85, those people with



other bad medical conditions, diabetes that's caused nerve damage or so forth, won't be a candidate for the most aggressive treatments.

Dr. John Krauss:

But yes, that's our hope that we would be able to then eliminate surgery. We've also looked at, and these results are not yet released yet, not released, but not even analyzed. So in other words, we've looked at for the higher rectal cancer, so those rectal cancers that are right on the junction, do they need radiation or not? And that trials completed accrual and within the next year or two we should know whether radiation adds something to those higher rectal cancers. My dream would be to make colorectal cancer something like Non-Hodgkin's lymphoma. So Non-Hodgkin's lymphoma is very rare in the rectum, but when you see it there, if it's a B cell, the typical Non-Hodgkin's lymphoma, you can just give chemotherapy generally six doses. It goes away in a very high cure rate. We have not found the secret sauce, the magic drugs, that work like that.

Dr. John Krauss:

My drugs will control the disease, but generally won't make it go away, except for very rare, less than one in a hundred times. And radiation and chemo pills together will control the disease, but generally not make it go away. The search continues for better medications. Now, it is exciting times because over the last four years, there's been 30 to 40 new drug approvals in oncology. And I guess the important part to remember is even rectal cancer, we're talking about one anatomic site of the body. And even rectal adenocarcinoma is going to work out to be 50, 60, 80 different diseases.

Dr. John Krauss:

So I doubt that I'll wake up tomorrow and find in my in-basket, oh, wait, somebody has discovered the new cure for rectal cancer. Because it's just so many different diseases. But we'll slowly pick away at this variant of it, that variant of it, as we get smarter to learn the variance. And that's been the really intellectually exciting part of being an oncologist over the last 30 years, is seeing these variants being picked up, seeing real strides being made. They released the statistics just recently that we've made another 2% gain against cancer. Part of it's people not smoking, but part of its real gains in getting stage four cancers into deep remissions that eventually can be under cures for some people.

Scott Redding:

So we've talked a little bit about some of the nutriments as it relates to hopefully helping with making quality of life better, replacing some of the surgical options. Are there other new promising treatments that you see coming down, or are currently out, that are across the board for colon and rectal cancer and maybe even other cancers? I know sometimes some medications and some treatment options crossover cancer types.

Dr. John Krauss:

The biggest thing that we haven't been able to elaborate for colon and rectal cancer is immunotherapy. So this has taken melanoma, which was a largely fatal disease, and put a number of patients, maybe as many as 40 to 50% of patients, into deep remissions. And us and other people across the country are working actively at trying to get ways to make immunotherapy work for colon and rectal cancer. And that will be hopefully an exciting lead, but it's taken a long time. The other way, besides getting harvesting your own immune system to fight the cancer, is to get at what's driving the cancer. So the really big home run has been we've known that chronic myelogenous leukemia, a rare leukemia, has one



mutation that always drives this cancer called BCR for breakpoint cluster region, Abelson virus. And so this one gene, abnormally expressed, causes this disease.

Dr. John Krauss:

And we've shown that Amit and Alactinib and Disatinib will put this cancer into a deep remission. In some cases, the people can even come off the drug indicating they might be cured. And if you look at the evolution over my practice, in other words, I went in 1988 up to University of Minnesota because I wanted to do bone marrow transplant. Bone marrow transplant was being done for chronic myelogenous leukemia. That was the most common reason the people were in a unit there. And then all of a sudden, 12 years later, we have a pill that puts people in a deep remission. A pill, that's way easier than bone marrow transplant. That pill is proven transformative. So then, okay. People were saying, "Well, that's just what we call liquid tumor. Those have always responded bad or we've cured leukemia in kids for a long time."

Dr. John Krauss:

Those are, I'll say, easier cancers. Of course, they're not easier for the person that has it, but that was kind of the knock on that. And then people discovered these other driver mutations called NTRK, one, two and three. There are three versions of this gene. And they were first discovered in colon cancer cell lines, but they turn out to be not that common in colon cancer, maybe one in 500, in a thousand. And these NTRK drugs, Interactinib, is the one that we work with here. And we've shown that with this pill just by itself, that we can put these cancers into a deep remission. And some of these remissions are lasting for months to years after the patients come off the medication. And so maybe these patients are cured. Maybe they'll have to be retreated. It's still early times. It's not years to decades, but this is very exciting.

Dr. John Krauss:

And then recently I was part of a publication that looked at the most exciting drug I've ever worked with in my career, a drug called Sitorasib, or AMG Amgen 510. And this drug works against the target called K-Ras. K-Ras is known to be a driver and cancer for a long time. And nobody's been able to target this mutation without making the patients very sick. The company came up with a drug that targeted a specific flavor of a K-Ras called, K-Ras G12C.

Dr. John Krauss:

This happens in about 13% of lung cancers and 4% of colon cancers. And this drug is just simply amazing. It is overall very well tolerated for both lung cancers and colon cancers. We've seen some dramatic responses. The medications not yet approved. I don't have any knowledge about the approval process to keep the investigators, and the approval process separate through the company pipelines. But the results I've seen with some of my patients, and the results I've seen with lung cancer patients, and the results that were published in the new England journal of medicine article, are just really amazing. Patients tolerating this medication very well, feeling better within a few days to a few weeks coming off oxygen.

Dr. John Krauss:

Now, it's not probably going to cure very many people, but to have something that works so well, to have something that people have been working on for 30 years, and we finally have a small niche in, will



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really drive a lot more effort in this area. So I'm excited about continuing to develop this area of specifically targeted molecular agents that will knock down a tumor.

Scott Redding:

Well, I really appreciate the time today as we wrap up. Is there anything that you want to make sure that the listeners walk away from this knowing that we've not covered? Or, that they take back to make sure they have the best care possible?

Dr. John Krauss:

Well, thanks Scott, for the opportunity to talk today. As you can tell, I'm really passionate about providing the best cancer care possible, the best cancer care for the patients in the state of Michigan and the upper Ohio area.

Dr. John Krauss:

My key message to both healthcare providers and people who find themselves having to be patients is really knowing exactly where the tumor is before any operative approaches. In other words, making sure that it's not unexpectedly in the rectum when it was thought to be in the colon. I think that's the key part of this because this area, the lower pelvis, is just so difficult to operate on. Once you've operated on it once the second and third operation become exponentially more difficult.

Dr. John Krauss:

We have just an absolute amazing surgical expertise here with all of our colorectal surgeons. So I'm honored to be able to work with all of them. But really the key message I think, is to know about before that first operation. Above and beyond that, I think being as informed as you can coming into appointments, making sure that you're staying generally healthy, walking around, that type of thing is key to a healthy lifestyle.

Scott Redding:

Great. Again, thank you very much.

Dr. John Krauss:

Okay, thanks a lot, Scott.

Scott Redding:

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