Announcer (00:00)
The following is an encore presentation of conversations on healthcare.

Mark Masselli (00:08)
When a patient hears they have cancer, it's often followed up with an appointment to begin radiation. But new research shows that more radiation for colorectal cancer patients is not the best option.

Dr. Alan Venook (00:21)
But clearly the vast majority of patients in this, in this popul, in this specific group of patients did not need radiation. And so obviously we spare them in the immediate toxicities as well as the long-term complications of radiation.

Margaret Flinter (00:35)
Our guest today is Dr. Alan Venook, who holds the Madden family distinguished professorship in medical oncology and translational research at the University of California at San Francisco.

Dr. Venook (00:46)
In the last decade, there's been a stunning increase in incidents in young people. And so it turns out that young people are less likely to go to the doctor for anything, let alone for rectal bleeding. Mm-hmm. And even when they go to the doctor, the doctors tend to dismiss it as well as not cancer, so hemorrhoids or whatever. And so we're seeing, unfortunately, young people who, even those who've reported earlier, symptoms tend to be more advanced by the time we recognize the cancer.

Margaret (01:15)
And this is Conversations on healthcare.

Mark (01:26)
Dr. Allen Venook, welcome to Conversations on Healthcare. Thanks. Thanks for having me. In March is, when we mark, colorectal Cancer Awareness month. Before we get into the results of your breakthrough study, I wanna ask you to explain the typical treatment for colorectal cancer. Its radiation treatment, and pelvic radiation in particular has many side effects.

Dr. Venook (01:53)
Right. So, colon cancer, which is cancer above the out of the pelvis, is really not, u radiation is not used. But for rectal cancer, which is cancer of the last 12 centimeters of the large intestine, chemo, chemotherapy and radiation and surgery have all been used typically for optimal management. Radiation has been popular and used for the last 30 or 40 years, perhaps to some extent, because it's difficult for surgeons to get good radial margins on their, on their, in their surgical field when they go into operate in the close confines of the pelvis. So that's sort of the rationale. But it's quite true for patients with rectal cancer. Historically, they get chemotherapy, radiation, and surgery, with all the consequences from those treatments.

Margaret (02:39)
Well, Dr. Venook, I believe the New England Journal of Medicine recently published, your research that suggested or demonstrated that less, maybe more when it comes to treating the patients. Now we're speaking just about rectal cancer, and show that many patients do just as well without receiving the radiation. Tell us about that. What are you seeing?

Dr. Venook (
Well, well, this was a study that was, we designed probably, 10 or 12 years ago, was run by Dr. Deb Deborah Schrag, who at the time was at the Dana-Farber, now at Memorial Sloan Kettering. And the premise was that if we chose our patients carefully, and built in protection to make sure we weren't putting them at risk, we thought that a good population really were being overtreated with, with, by the use of radiation. We think in, in many cases, cancer care evolves where we do more to get the best result we can and then start going backwards in terms of taking away therapy. So in this case, we designed a study in patients who we thought were the best candidates and likely did need radiation patients, let's say, with high rectal cancers, not cancers near where the, where the sphincter function of the bowel is. Patients who would normally have surgery and radiation and chemotherapy altogether, we, we, we thought we could design a trial that would just give patients chemotherapy, upfront as a randomization. And then, half the patients would get the standard treatment of chemo, radiation, and then surgery. So we did the study designing in such a way that they got chemotherapy.

We built in the protection that if they hadn't had market reduction in the tumor after four cycles of chemotherapy, we would go right to radiation and then surgery. So we didn't put them at risk for failing to cure a disease that was curable. And we found that, in fact, by doing that is a study over time demonstrated that there was no difference in overall survival. But, but most patients in this population did not need radiation. About 9% of the patients who we started out without doing radiation, we, we did add radiation because didn't get what we thought was enough of a benefit from chemotherapy. But clearly the vast majority of patients in this, in this popul, in this specific group of patients did not need radiation. And so obviously we spare them the immediate toxicities as well as the long-term complications of radiation.

Mark (05:06)
Alright I'm just a little dense on this. There's, but just to be a hundred percent clear on the question, you and your colleagues are convinced that there's no compromise in patient survival or the risk of recurrent cancer over time with less radiation.

Dr. Venook (05:20)
Well, so I think being convinced is different than being confident. So, the way I would put it is that we, you certainly need more follow up to be certain that we haven't, maybe there might be longer term consequences, but by statistical analysis, there's, it's, we found non-inferiority, right? So, so you can look for, for one treatment to be better than the other. Actually, it's harder to show that something is non-inferior. And we've, we definitely have shown that in regards to local control and, and progression, early progression, there's no difference. It's conceivable after 10 or 15 years, we might see a survival difference, I suppose, but no evidence so far. And we, we've got about five years of average follow up on all these patients.

Margaret (06:06)
You know, I'm gonna take us up, a level and we'll probably go back and forth a little bit between, treatment and prevention, in the show, if you'll, you'll bear with us. But you've, I think, provided an important message for our listeners about maybe separating out colon cancer and rectal cancer. Take just a moment, to, to share with our listeners what are the, the presenting signs and symptoms of colon cancer versus rectal cancer risk factors, and we'll, we'll talk about screening a little bit further on.

Dr. Venook (06:36)
Sure. So, the, the general sensation sense of these of colon and rectal cancer is a change in bowel habits. And most commonly, let's say bleeding, finding blood in the stools would be the most, most thing, most disconcerting, and most thing that is most likely to har that signal that there's a colon or rectal cancer. Although most rectal bleeding is not associated with colon or rectal cancer, but it certainly should raise your index of suspicion. Family history is, is very important. If you've had one, or if you had one first degree relative, you're at greater risk. If you've had two first degree relatives, you're at very high risk for, for, for colon or rectal cancer. And again, the symptoms are often dismissed by patients. So either because they want to ignore them or they just don't think it's a big deal. Right. So, so bowel, you know, di intermittent diarrhea and constipation, a con, you know, some crampy pain, for example, as I said, bleeding being one of the most common things that's noticed. One of the most, the problems we're having now is there's a, a distri, the distribution of patients who are getting colon and recal cancer has changed. And the last decade, there's been a stunning increase in incidents in young people. And so it turns out that young people are less likely to go to the doctor for anything, let alone for rectal bleeding. Mm-hmm. And even when they go to the doctor, the doctors tend to dismiss it as well as not cancer, so hemorrhoids or whatever. And so we're seeing, unfortunately, young people who, even those who've reported earlier symptoms tend to be more advanced by the time we recognize the cancer. So, so this is a, it's a sort of a changing paradigm in terms of who we have to think about and, and our index of suspicion mm-hmm. For who's going to get colon and rectal cancer.

Mark (08:26)
The American Cancer Society in the US preventative service task force, which we sort of think about as the gold standard, recommend that colorectal cancer screening begin at age 45 for asymptomatic average population. But the American College of Physicians says the screening should start at 50. I think this is conflicting guidance to the public and some of your fellow, physicians say it does a disservice to have such confusion. What advice do you have?

Dr. Venook (08:55)
Well, I agree it does do a disservice. The, the, the challenge, and I think the American cancer societies change from 50 to 45 a couple of years ago, was based on modeling, where they, they recognize that there's a, a greater incidence in younger patients with who developing colorectal cancer, and they sort of, sort of thought about how

many people this included and what was realistically achievable. I'm not sure that that 45 or 50 is the right time benchmark. As I said, we're seeing a lot of patients in the age range of 35 to 40, and you're not gonna find cancer early if you don't screen until 45. I, I think we're missing the boat a little bit on this, on this approach of colonoscopic colonoscopy to screen, or even fecal occult blood. I think what we have to do is, is determine if there aren't some circulating factors that tell us who's at greater risk for having colon or rectal cancer, sort of enrich the population for patients likelier to have the disease, and then try to screen that population. Because I think clearly a, a global strategy, you know, you just can't do enough colonoscopies to screen all the 40 and 35 and 45 year olds. So, I think we should do what is achievable rather than what, what we wish we could do. I must say, in our approach to screening people over the age of 50, we've been quite successful in really markedly decreasing the risk of colon and rectal cancer in patients over the age of 50. Even if the penetration of that screening is maybe only 60% of patients get the proper approach and, and are checked for the risk of, for the possibility of colon rectal cancer, that's enough of an intervention to decrease the incidences quite markedly in patients above that age. So we could do this, this, do the same with younger people, except you just can't be doing colonoscopies and all the young people that they're around.

Margaret (10:57)
Well, we can certainly speak from the, primary care space, community health center space, taking care of large, populations of individuals for whom screening may not be the highest priority. And we'd love to give you a chance to, maybe just speak to the value of, doing the at-home tests that we now have available. Certainly they've, improved over the many years that, I've been in practice. What can we do to get more people to engage in, in doing a screening test at home, at whatever age level we set as the appropriate one for screening in the absence of family history? Well, that you add, that's a $64,000 question. I hope you have the answer. Maybe $64 million question given inflation.

Dr. Venook (11:41)
You know, I, I, I don't know. I, it is penetrating that, that pop the population of patients and people telling them, getting them to believe that they could, should do this is very difficult. It's always stunning to me how hard that is. But let alone trying to change their diet or do other things that might have, have bearing on this, I think it's incumbent on primary care physicians to actually emphasize this and push this. And my disappointment is that many primary care physicians don't really see this as a focal point. But I don't know, I don't know how to get convince people that there're these, these sort of un these sort of unpleasant things. Let's say it's taking a sample of stool and putting it on a, on a card, like exactly why that's so unpleasant. I don't know. But, but it's very hard to convince people to, to, to do that. The tests are not perfect, but it certainly, they'll help, they would help to identify some patients who could avoid bad disease and early death because of, a cancer. Mm-hmm. One of the things that I do think is, is lax is, is interesting how many patients we'll see for second opinion who've been diagnosed with colon cancer. And you look through the records and nobody's taken a family history. And that's, that's at least a place where we should all be starting.

Mark (13:13)
You know, I wanna pull the thread on your comment about diet and what's the impact between, a vegetarian diet and other diets in terms of, contracting, colorectal cancer?

Dr. Venook (13:13)
Well, certainly so-called western diet, which is like it, let's say burgers and fries. Those are, that's not good that it clearly increases the incidence of colon and rectal cancer. In contrast, a non-Western diet, fruits, veggies, those have a lesser in those people who have those diets have less incidents, but it's not absolute. One of the things I'd say is the, for example, the change in the young, young patients getting colon rectal cancer, these are not people necessarily with different diets. They're vegans. There are triathletes that, you know, there are all sorts of, there are people who, who would you think not have the standard risk factors for cancer who are getting cancer at a young age? But with, as with everything else, smoking, for example, is a risk factor for colon cancer. As I said. High, high, you know, high fatty foods, red meat, those are all things to avoid. But, none of them are, patients obviously follow all those rules and still can get colon cancer. I think the driving forces probably heritable risk that we can't quantify or don't understand that is the greatest cause of colon cancer.

Margaret (14:29)
Well, Dr. Venook, we, we hear so much about, in many disease states, the ability to maybe transition from some of these tests like the colonoscopy or the, at home test Is there any hope of a blood test marker, at some point down the road? Or is the research underway in that area?

Dr. Venook (14:54)

The research is underway, and I think we're closing in on something that might actually be able to tell us who has polyps. I think we're close to that. Now part of the problem is, is, is appropriately, it's been studied mostly in older individuals like you and me. Well, at least like me. That's okay. You can include me too and all of us. So, right. And so, so looking in the population of, let's say, above 55 or 60, and identifying a, maybe circulating factors circulating DNA for tumor, DNA, for example, that might be a handle on finding people who have early cancer. Certainly we're seeing that there are number of diagnostic tests that are out there that are being used and, and not, not really by any means incredibly effective, but we are finding some early cases. I think as we, as we hone down on that, we're likely to find a, a, a, a series of DNA findings that might tell us who's at risk. The problem is gonna be understanding if, if what we learn in 55 and 60 year olds will apply to 35 and 40 year olds, because we've been relatively successful in, in getting screening colonoscopy into patients above the age of 50, and the patients, the young patients, where that's really where we need major strides. And I think a blood test would go a long way towards helping us figure out who, who we should be focusing our, our screening on. And, but we need to do the work to prove the young populations diagnostic companies are doing that. They're probably a dozen different diagnostics companies working with amazing technology to look for genetics, cancer, cancer genes, et cetera. And I do think that we're closing in on, on something that'll be practical and useful down the road.

Mark (16:34)
Are you talking about some gene editing, CRISPR technology that might sort of be able to be applied here that, you know, as we move down the road with more understanding?

Dr. Venook (16:46)
Well, I think, you know, CRISPR, I, it's a good question. I think possibly CRISPR will have more of a role in, in replacing genes or, or, or getting, putting genes in that for function, loss of function. Mm-hmm. I mean, the story about sickle cell is kind of amazing. Right, Right. Absolutely. But no, I think I'm thinking more about a, a looking at a fingerprint, let's say, a series of molecular of features that may characterize a, an early cancer. And if you find you can find cells that have particular mutational patterns, I mean, it's like finding a needle in the haystack, but it's remarkable what the technology can do. There, there's a test, for example, you can, if you have a patient has a cancer, you can create a probe that will find a cell, a, a bit of DNA in the blood of that patient that has the same molecular features as the cancer. It's just astounding technology.

Mark (17:45)
Is that also being fueled by some of the AI stuff that's in the background on, on, looking at these large data sets and being able to call through them?

Dr. Venook (17:56)
And I think the answer ultimately will be in ai, because if you, my bet is we already know that we would know what some of these risks are, but we're not smart enough to figure it out. But I think to that end, I think the most important step we all need to take. And one of the things we're pushing for is further to be a single public database. Mm-hmm. Of all the information we gather on, on patients at risk or patients with cancer. And we're advocating for it, obviously the privacy and other issues. But I think that overall, the benefit, and this is worldwide, because interestingly, there are increased incidents in colon and rectal cancer in young people is not just in the us. Mm-hmm. It's, it's everywhere. And so, so there's obviously a changing dynamic that, that there's, it's probably an explanation for if we had enough smarts to figure it out.

Margaret (18:45)
I, I was just, thinking Dr. Venook, that I we're kind of traveling in the conversation from what would seem like the simplest thing in the world, you know, do that, stool card as I still call it, the at-home test to ai, and technologies that we're still hoping for and don't yet have it in the, in the diagnosis and treatment. And I, I wonder, thinking back to when the Affordable Care Act was passed and how excited I was, that finally if something was on the US Preventive Services Task force list, it would be covered by insurance, no questions asked, no deductible, no copay. That seemed to me like it was gonna be a real game changer for cancers like colorectal cancer. But we haven't, we haven't seen that. So I'd like to ask you, in your work with colleagues and conferences and your research, any groups that are really getting it right in terms of getting populations of patients to do the test, what have you seen CDC have anything to show us? Do you have anything to share with us?

Dr. Venook (19:45)

Well, no. I mean, that's really disa it's been disappointing. There, there are some examples where the testing has been really very effective. For example, the state of Delaware, maybe 10, 12 years ago, they are, they, of course, Delaware has like one congressman and two senators and the governor, they all know each other, and they sort of keep change the sort of exchange jobs. But it, it is, it is a state that more or less is dominated by a couple of employers. And the state of Delaware, where, which had a very high risk of death in African Americans from colon and rectal cancer, set out to see if they couldn't eliminate colon and rectal cancer. And actually by, by in-depth penetration of the population with the aid of the city governments, the, and the major employers, they almost eliminated colon cancer over the course of a couple of years. Really astonishing. And that's an example of what can be done if you have a will and you have a relatively captive audience and a small, and, and so the answer is it's doable, but you really have to mean it. And I think, it's hard. It's not easy. And some populations, let's say with, with captive patients, let's say HMOs, they should be able to do it. But, but even getting those people who are there, who are limited in where they can go, the compliance with these screening tests is just not adequate so far. So, I, I think it's doable, but it really takes a concerted effort by a lot of people.

Mark (21:15)
Delaware, Maryland always has sort of advances going on. There's something in the DNA in the water there. You know, I do wanna pull the thread on your talk about special populations. And as you know, 90% survival rate with early detection and treatment, but really these disparities in this population that we're very concerned about, and I know you are as well as particularly Black Americans, American Indians, Alaskan natives, underserved Americans, disproportionately affected by disease. What do you see as the solution to closing these gaps? Obviously, you got an exemplar in, in, in Delaware, but what's, what other thoughts do you have about the, reaching this very important population?

Dr. Venook (21:56)
Yeah, that's a great question. And we've, we've ta taken a variety of strategies at UCSF, where, where I'm located, where we reach out into the community. We, we try to have a presence in the African American community. We have a large Hispanic population. I, the, it's very hard to make inroads. Part of it is maybe trust. I think there's, there's a, a fear amongst many populations that, that we're, we're jerking them around. We're not really, we're not really trying to help them. Mm-hmm. Mm-hmm. It's, some of it is cultural. Some, some things that people won't talk about. We're, we're trying. And I think, but it's, it's been not, it's been hard. One of the things we are now doing is going into the, into the communities with people who speak their language, people who look like the people in the communities trying to, to get the message across. Very difficult to do. There's years of, I think, mistrust and years of neglect that it's hard to, to fix. You know, it's one thing to, let's say if you're looking to do prostate cancer screening with a blood test for PSA, let's say you can go to where, where African American men might congregate wherever that might be in a community, let's say an African, largely black community. But doing screening for colon cancer is, is not as simple. Mm-hmm. And, and so, so, not a, I can't really say we've been very successful at it, we're trying. Mm-hmm. But I think our current belief is that we need to have people of the members of the community Yeah. Do the, try to do the recruiting or the convincing that it's worth doing.

Margaret (23:36)
Well, that's certainly a large focus for our research institute as part of the Moses Weitzman Health System, which is very focused on health, equity, health disparities, and making sure we reach into our population. So we'll keep you posted on a research, in that area. And it is, it is always a tragedy when there's a late diagnosis, where the, earlier diagnosis would've predicted a better outcome. But we always look, to see whether there are breakthrough drugs. I know in late 2023, the Food and Drug Administration approved a new drug to treat refractory metastatic, colorectal cancer. What are we learning about that? And are there other things in the pipeline that you see coming, when treatment is the option?

Dr. Venook (24:21)
Right. So the drug you're talking about is drug called tib, which is a, an oral inhibitor of the, of a vascular, fa vascular factor that need to, to grow. And that's a, that's a, a, these new drugs are helpful. Certainly for some patients, they'll get meaningful benefit. On average, though, I think we're, if we want to be bold, we'd look for something that's more dramatic or more impactful. Yeah. The one thing that's been very frustrating about colon and rectal cancer has been the, the lack of efficacy of the immune therapies. Right. If you look at what's changed the world of cancer in the last decade, it's been the checkpoint inhibitor, the, the understanding of how the body, how the cancer sort of takes the body's mechanism for protecting itself from autoimmune disease and, and hides the cancer can hide behind the, the, these factors. And so new immunotherapies that go, that are able to get around that blockade have changed the face of melanoma, of lung cancer, lots of cancers not so much in colon and rectal cancer, except for the small subset of patients who have gene, who have what's called lynch

syndrome, or M or MSI high have, have microsatellite unstable cancers. The real trick in colon and rectal cancer to make a difference will be figuring out how the immune system can be somehow alerted or made able to recognize the presence of colon and rectal cancer. And that's our focus for research. And, so far, not, not the progress we'd like, there are a couple hints that we're on the way, but so far, colon rectal cancer has remained really di really impossible to get at in that way. Maybe not surprising if you think about the ba the colon is bathed in bacteria and fungi and viruses, all sorts of flora in the, what's called the microbiome. And so the body has sort of somehow or other, basically protected the colon from the immune system, because if the immune system were attacking all these foreigners, we'd be sick all the time. Mm-hmm. Well, it turns out that that may be the reason that these, these immune system doesn't affect cancers because there's, the, the immune system just isn't as active in the colon. That's sort of the, that's the, the, the practical implications of, of how we, how our bodies work.

Mark (26:43)
Well, we know there's a lot of work going on in the microbiome world. Jackson Labs up the road from where we are, and others around the country are working on it, but they all work on it because we've got federal government support, or we hope we do. 'Cause it plays such a large, role in cancer research funding. But we're on the verge of another budget shutdown. I'm wondering how do you see cancer funding and, how well you think the dollars, will be spent or are being spent?

Dr. Venook (27:16)
Well, that's a, that's a, that's a moving target. I actually sit on a committee with the American Society of Clinical Oncology that spends a, a couple days every three or four months on Capitol Hill. And, and of course getting people, getting the folks on Capitol Hill interested in this and good luck. I mean, there's not a lot of interest. Now, the new head of the NIH is Monica Burley. Yeah. Who is a cancer surgeon who, who actually was one of the principals behind the, the cancer study we talked about right off the bat, the rectal cancer study. She was one of the co-authors. She chaired the, the group that led that study. So, so the people get it, and I think they understand where the focus needs to be, but, but having said that, we, we, we worry always about the, the cuts. I, to me, the greatest danger is that we're gonna lose our young population. The young scientists who will, will continue on from people like me when I'm, when I'm, when I move on, who's gonna carry the, who's gonna be carrying the baton, and the poor funding or inadequate funding going forward puts the, those pe those individuals at risk for whether they can spend their careers doing what I've been able to do. Mm-hmm. I think that's my greatest fear. I do think we're on the cusp of big advances, because if nothing else, AI should give us a, a, the ability to figure out things that we've been unable to figure out so far, but we have to have folks still engaged to, to make those, those discoveries.

Margaret (28:48)
Well, Dr. Venook, we wish you much success in your ongoing research and also want to thank you for all of the care and commitment, that you've made throughout your career in this area. And we wanna thank, both you for joining us, but also our audience for being here and being part of this important conversation. Be sure to subscribe to our videos on YouTube. Find us on Facebook, and X with our account name, CHC radio. And as always, go online to chcradio.com to sign up for email updates, and please share your thoughts and your comments about this program. Dr. Venook, thank you again so much for your important work and for this conversation.

Dr. Venook (29:26)
Thanks for giving me the chance. Take care everybody.

Mark (29:28)
That's Great. Continued success.

Dr. Venook (29:30)
Thank you so much. Bye-bye.

Margaret (29:37)