00;00;00;02 - 00;00;41;08 WNPR (Radio voice) Funding for Yale Cancer Answers is provided by Smilow Cancer Hospital. Welcome to Yale Cancer Answers, with the director of the Yale Cancer Center, Dr. Eric Winer. Yale Cancer Answers features conversations with oncologists and specialists who are on the forefront of the battle to fight cancer. Here's Dr. Winer.

Dr. Winer Tonight, we're going to be talking with one of my colleagues in radiation oncology, Dr. Ranjit Bindra, about cancer of the brain, which is one of the most complex and difficult types of cancer to treat.

00;00;42;01 - 00;01;24;08 Dr. Winer There are a number of different types of brain tumors, but the most aggressive of those that is glioblastoma is one that continues to challenge us. And there is much research going on both related to glioblastoma and to other forms of of brain tumors, which will be touching on as well. So I'm very pleased to welcome Dr. Ranjit Bindra, a physician scientist at the Yale School of Medicine, co-director of the Yale Brain Tumor Center at Smilow Cancer Hospital and the leader of the Bindra lab at Yale.

00;01;26;06 - 00;01;59;13 Dr. Winer Dr. Bindra is very much at the forefront of brain cancer research, and his laboratory has done pioneering work. So we'll talk about a whole range of subjects. Ranjeet. Thanks so much for being on with us this evening.

Dr. Bindra Thanks so much for having me. It's a real pleasure.

Dr. Winer So maybe you could just start by introducing the listeners a little bit to you. 00;02;00;11 - 00;02;31;27 What got you interested in both radiation oncology and what got you interested in brain tumors?

Dr. Bindra Yeah. Well, thanks so much for having me again. I started my journey long ago. Connecticut native went to Yale as an undergrad and then came back here for my M.D. Ph.D. program. It was during that time I was working in our now chair, Peter Glaser, in his laboratory, and my father had actually been diagnosed with metastatic esophageal cancer.

00;02;32;06 - 00;02;57;17 Dr. Bindra But halfway through my program, it was there that as I was working in a basic research laboratory on things like DNA repair and the tumor microenvironment that I got very, very personally inspired to work on cancer. Soon went on to Memorial Sloan-Kettering to do radiation oncology residency and a postdoc at that time and came back to Yale. And really, that was the beginning of my journey in this area.

00;02;58;06 - 00;03;30;28 Dr Bindra Yeah, you know, it is remarkable how many of us have some sort of cancer history, either ourselves or in the family or what have you. Of course, cancer is common, so many people in the world have experience with cancer, but I think it's probably a slightly higher proportion of people who work actually in the cancer field.

Dr. Winer So as a physician scientist, you are both a laboratory scientist and a clinician. 00;03;30;28 - 00;04;08;14 And I might add a clinical researcher as well.

What part of that work stimulates you the most, or is there no single part?

Dr. Bindra I think it is actually being able to jump between all the different worlds. I'm constantly inspired by patients encounters. They stimulate new ideas and thoughts, which I can kind of rush back to the clinic from the clinic, rather, to the laboratory, and bring those ideas, those complex problems that we can then solve in the laboratory and then bring them back to those patients.

00;04;08;14 - 00;04;34;29 Dr. Bindra And it allows me to tell patients when often they'll say, you know, is there hope in the future? And I said, you know, we're working on this. And that's something that gets me very excited to operate in those different worlds.

Dr. Winer You know, we've had a relatively limited number of radiation oncologist on this show. Part of that is because there are fewer of all of you than there are surgeons and medical oncologists.

00;04;35;19 - 00;04;59;29 Dr. Winer But maybe you could just help people understand a little bit about how radiation works.

Dr. Bindra Yes, certainly. We always spend a lot of time with our patients discussing this because it can be an area of fear for patients. And they often ask, you know, will I be radioactive when I come out of the facility? And we often say, you know, think of it as a light switch turning on and off.

00;04;59;29 - 00;05;20;15 Dr. Bindra And when you're a kid, if you ever broke a bone and you got an X-ray, it was really the same thing. It's completely painless, noninvasive way to damage tumor DNA. And we try to protect the normal tissue a lot like chemotherapy in many ways. But we can focus those X-rays on the specific areas that we want to treat while sparing the normal tissue.

00;05;21;25 - 00;05;57;29 Dr. Winer Yeah, and there are situations, though, and I realize this isn't, to the best of my knowledge, generally done in the setting of brain tumors. But there are situations where people are somewhat radioactive after treatment because the radiation is actually implanted in them. Can you just comment on that sense?

Dr. Bindra Yes, it came up. Yeah. Now that great point to the one exception, what we call brachytherapy, which is a way to put seeds that emit a little bit of radiation just in the area that we'd like to treat.

00;05;58;07 - 00;06;28;04 Dr. Bindra There's also something called radiopharmaceutical therapy, where patients can get antibodies more often, antibodies that have radioactive conjugates in them that they get injected into the body, and then those antibodies deliver the radiation for some period of time. They'll be locally radioactive. But we always advise our patients how to sort of manage that.

Dr. Winer Sure. And for brain tumors, how has the area of radiation changed over the years?

00;06;28;27 - 00;07;01;07 Dr. Bindra I think this is a particularly exciting area for us with advances of technology like proton radiotherapy, which soon will be at our facilities here in Connecticut, were able to precisely scope the radiation beam specifically to target the tumor. In the past it was very difficult to localize things. Are imaging technologies were limited are what we call our onboard imaging technologies where we take a picture of the brain, the normal structures in the tumor, for every single treatment.

00;07;01;07 - 00;07;31;22 Dr. Bindra And even if the patient moves one millimeter one way or one direction or another, are able to adjust dynamically the radiation beams. And so there's a lot of advances in both getting more precise radiation that's also less toxic to the normal tissue.

Dr. Winer And of course, when we're talking about the brain being tighter with your fields, that is having the fields directed at the tumor as opposed to the normal brain becomes particularly important.

00;07;32;20 - 00;08;14;18 Dr. Bindra Exactly. Can make miles of a difference, as we would say, in terms of long term cognition and preserving function. And so while we're in general issues about radiation, so there's the new proton approach and there will be a proton facility that we will that we're very much part of here at Yale, in addition to some other hospitals. But then there are there are these two other particles that are often talked about electrons and photons.

00;08;14;18 - 00;08;40;05 Dr. Winer And talk about the difference between these things. I mean, for even for me, much of this is pretty murky.

Dr. Bindra Yeah. I always I have an analogy that I use in the clinic that generally works well is if you think about throwing a ping pong ball against a wall and you've got a pillow on the wall and it's sort of a weird analogy, but when you throw that ping pong ball against that pillow, a proton particle is like that ping.

00;08;40;15 - 00;09;15;06 Dr. Bindra It stops right there and doesn't go any farther past it. Okay. Photons can actually go way past that. Go right past that pillow almost through the wall and sort of die off almost like a sound going across the wall. Electrons are a little bit different in that they're sort of sprinkling doses that stop immediately on contact. We can't deliver them deeper than the skin, a couple of inches, whereas protons, you can precisely localize them really anywhere in the body and literally the beam will stop right at the edge of where you're prescribing the dose.

00;09;15;06 - 00;09;48;00 Dr. Bindra So incredibly precise tissue distributions.

Dr. Winer So if I'm getting this right with photon ends, which is sort of for the most part the usual form of energy that's used for, for radiation, you can deliver it, it whatever depth you choose to deliver it to. You can't control that. It's precisely to that depth, which then leads to potentially somewhat unpredictable toxicity.

00;09;48;10 - 00;10;18;05 Dr. Winer Whereas with where with protons you are much more precise about that. Am I getting this right?

Dr. Bindra You've got it. You got it. Exactly. And I think there's certainly some cases where those differences make a huge difference overall in toxicity and efficacy and some areas where there probably isn't much of a huge difference, relatively speaking, especially in children. For instance, we need to use protons because these children will have 40, 50 years of life ahead of them for a secondary cancer to arise.

00;10;18;05 - 00;10;59;05 Dr. Bindra And so minimizing the dose becomes absolutely critical. And, you know, I think that what many of us don't realize is quite how costly some of these facilities and machines are.

Dr. Winer And just to give people a sense for a proton facility and it's usually a facility that that sort of stands alone with just one machine in it, give us a sense of the price tag just so that the sticker shock that I once experienced everyone can feel.

00;10;59;18 - 00;11;21;22 Dr. Bindra Yes, it is. It is surprising. First, we like to note it's about a football field, in many cases, size depending on the facility and can be anywhere from 50 to 100 million to up to $250 million because you've got to accelerate these protons at such high speeds and then localize them. It is remarkably expensive, but it is surprising when I discussed that.

00;11;22;04 - 00;11;45;25 Dr. Winer And why does it have to be the size of a football field or close to it even? I mean, that's huge.

Dr. Bindra Yup. And it's just like when you hear about those physics' particle accelerators in Switzerland where they've got to rotate and sort of steadily increase the speed of the particle so they can get to a range which can be actually useful to deposit energy into a tumor.

00;11;45;25 - 00;12;21;00 Dr. Bindra So you actually have to have a large, large area to do that well.

Dr. Winer So when we talk about brain tumors in general, we're talking about potentially three different disciplines involved. There are surgeons or neurosurgeons, and in this case there are radiation oncologists and then there are neuro oncologists who typically get involved in giving drugs of various sorts. And you all collaborate together.

00;12;22;07 - 00;12;58;29 Dr. Bindra And this is why I love our field is in neuron in the world of the brain tumor space. We all work closely together to figure out, do we need all three modalities to modalities? You know, what is the combination? And it's a really highly collaborative process and at least for patients who have glioblastoma, the most aggressive form of brain cancers.

Dr. Winer What proportion of those patients really end up seeing a neurosurgeon or radiation oncologist and a neurologist and wind up getting all three different types of treatment?

00;12;59;15 - 00;13;19;16 Dr. Bindra We would say it's very important, especially at Yale. We have a multidisciplinary tumor board and a service where you pretty much see all three of us, and I think you need the perspectives from each of those doctors. I'd say in the end, the majority of patients will get surgery, a large fraction will get radiation and an equally large fraction will get chemotherapy.

00;13;19;16 - 00;13;48;04 Dr. Bindra And then all three is quite common for GBM. In fact, it's the standard of care to get all three.

Dr. Winer Yeah. Now what I failed to mention or ask you about is the role of other types of professionals. So people who may be speech pathologists to help people who have language problems… nurses, social workers, it's really a whole team approach.

00;13;48;04 - 00;14;08;19 Dr. Bindra It's unbelievably complex. And you think about the radiologists looking at the images, pathologists looking at the actual tissue, and then the nurses and everyone else involved. It takes a village.

Dr. Winer Well, we're going to have to take just a brief break. When we come back, I'm going to ask a few questions about other kinds of brain tumors.

00;14;08;19 - 00;14;41;25 Dr. Winer And then we're going to get into your research and some of the newer drugs that may be on the horizon. All right. We'll be right back with our guest. Dr. Ranjit Bindra, a radiation oncologist specializing in brain tumors.

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00;15;27;23 - 00;16;02;26 WNPR Tumor gene analysis has helped improve management of colorectal cancer by identifying the patients most likely to benefit from chemotherapy and newer targeted agents, resulting in more patient specific treatment. More information is available at Yale Cancer Center dot org. You're listening to Connecticut Public Radio.

Dr. Winer Welcome back to the second half of Yale cancer Answers. I'm Eric Winer. And tonight, I've been speaking and will continue to speak with Dr.

Ranjit Bindra, a physician scientist who focuses on brain tumors.

00;16;03;18 - 00;16;46;16 Dr. Winer So we've been talking generally about radiation, a little bit about brain tumors. And the brain tumors we talked about are largely the most aggressive brain tumors. That is a blast. But in fact, there are other types of brain tumors as well. And these are graded in terms of aggressiveness. Maybe you could educate us a little bit about the different types of brain tumors, because I know that some of your research focuses on both glioblastomas, but also on less aggressive brain tumors.

00;16;47;05 - 00;17;18;05 Dr. Bindra Yes, certainly. So we always classify first brain tumors as sort of intrinsic or extrinsic intrinsic meaning coming from the brain tissue and extrinsic coming from other parts of the body. We call those brain metastases. But in the intrinsic category, there's a pretty wide range of diverse tumors that often are classified based on the tumor tissue, the normal tissues that they come out of, some of the peripheral surroundings of the brain can often cause benign and sometimes malignant tumors.

00;17;18;05 - 00;17;41;27 Dr. Bindra We call those meningioma. We also have the pin. The more linings of the brain, which we call the pin, the moments when they become cancer. And then even within glioma, which is really in that the brain tissue itself becomes cancer. We have four great discrete one, which is essentially benign grade two and three which are low and high grade, and then grade four, which is often called glioblastoma.

00;17;42;21 - 00;18;14;20 Dr. Winer And for patients who have grade two and three gliomas, oftentimes these are individuals who live with these tumors for an extended period of time. Is that correct?

Dr. Bindra It is correct. Many of these patients are either and present at a young age, and the tumors can kind of smolder along for ten, 20 years. Sometimes some of them are slow growing and probably had started in their twenties and thirties and suddenly they present in their forties or fifties, incidental finding or whatnot.

00;18;14;24 - 00;18;41;19 Dr. Bindra But there's a pretty wide range.

Dr. Winer And just in the past couple of years we've seen the approval of a new drug, one of the first to get approved for the treatment of these brain tumors. Can you tell us a little bit about that?

Dr. Bindra Yeah, it's a very exciting time In our field. We're starting to see FDA approvals in this space at a rate that we've never seen before in grade two and three.

00;18;41;19 - 00;19;12;29 Dr. Bindra Gliomas, particularly grade two, that 70 to 80% have a mutation in a gene called H involved in cellular metabolism. And there's now a drug that targets that of targeted therapy for these grade two gliomas, which is really exciting for patients.

Dr. Winer Yeah, no, I mean, it was so exciting a couple of years ago that, that when it was initially presented it was on a large plenary session at our biggest cancer meeting.

00;19;12;29 - 00;19;47;12 Dr. Winer And I think everybody was just thrilled to see this kind of advance in in brain tumors. So maybe you can tell us about your laboratory and the kinds of studies you're doing in the and the types of drugs that you hope will come out of that.

Dr. Bindra Yeah. Thank you. So are laboratories focused on finding specific mutations in cancers and often, most often brain tumors where we can develop a way to exploit the defect.

00;19;47;12 - 00;20;15;17 Dr. Bindra What we realize is that cancers often acquire mutations to become cancer, but then those mutations themselves become an Achilles heel that we can go after with a drug and this is what people think of as synthetic lethality to some extent, correct. In breast cancer and ovarian cancer. The classic example, there's a drug called a Part B inhibitor which targets the BRCA mutation.

00;20;16;07 - 00;20;57;22 Dr. Bindra And that is exactly the type of approach that we take in our lab. But for brain tumors.

Dr. Winer So you go after what makes the cancer, the cancer, so that you can basically cut off its ability to remain a cancer.

Dr. Bindra Exactly.

Dr. Winer What are some of those genes that you've been able to identify? What do they do?

Dr. Bindra So very interestingly, the idea of mutation that I mentioned earlier, several years ago, we actually showed that PARP inhibitors that are usually used for breast and ovarian cancer, particularly the BRCA mutation, as we actually discovered in our laboratory, that the mutations induce sensitivity to that class of drugs.

00;20;58;10 - 00;21;27;18 Dr. Bindra More recently, another biomarker called MGMT, which is silencing about half of GBS, we developed a next generation set of drugs that target that biomarker. We published that paper in science and we're now trying to translate that into the clinic.

Dr. Winer And when these findings are translated into the clinic, what's involved, how long is this process? You know, what's the fastest you think it could be and what's the typical.

00;21;28;08 - 00;21;48;28 Dr. Bindra Yeah, I think this is an it was been a humbling experience for me trying to translate work from bench to bedside. You realize not only is it hard to make a discovery, to find a target, to find a drug against it, but actually to bring it all the way to patients. Typically you'll hear numbers of years on the order of 15 to 20 years.

00;21;48;28 - 00;22;18;07 Dr. Bindra I started looking back recently at this. Now we're finding 10 to 15 years. And I think even more exciting, we could probably get this down even ten years. But even ten years is a long time. But it's needed because it's so complicated to bring drugs from the bench to the bedside. But at least as a as cancer doctors, I think, you know, you and I would both agree that if we could figure out a way to get that down to five years, so much the better.

00;22;18;20 - 00;22;43;07 Dr. Bindra And, you know, some of it ends up being about frustrating delays, delays getting clinical trials up and running. And of course, when you do a clinical trial, you need patients to participate.

Dr. Winer And so if you don't open this study and enough centers, you're not going to have enough patients, correct?

Dr. Bindra Correct. It's one of those types of things.

00;22;43;07 - 00;23;27;14 Dr. Winer And at the cancer center, as you know, as our leader, we've been spending a lot of time on this. And I think we are making progress and we are seeing lots of collaboration across different institutions in the ability of pharmaceutical industry, biotech and academia to all work together to get drugs faster to patients. Now, you've also had the experience of being involved in starting some biotech companies, and I think many people find that necessary to get the work done because, of course, academic institutions are places where we take care of patients and we do basic discovery.

00;23;27;14 - 00;23;56;15 Dr. Winer But that whole process of developing a basic finding and making it into a drug and testing that drug is not really well-suited for a university oftentimes.

Dr. Bindra That is correct. And I think every Thursday I see patients in clinic brain tumor patients, and it reminds me of the urgency. And I'm an impatient person by nature and I love all the work we do in the academic setting.

00;23;56;15 - 00;24;16;13 Dr. Bindra The goal isn't always to develop a drug and get it into patients. And often we need to go by creative routes like the entrepreneurship startup route that's moves often at light speed in terms of bringing ideas by deploying capital large amounts of capital in a very focused manner to develop that idea into a drug and get that drug into patients.

00;24;16;20 - 00;24;45;29 Dr. Winer Often the biotech world is where we need to move for that. I suspect that our listeners can hear both in the content of what you say and the way you say it, that you're both, as you said, a little impatient, but also somebody who wants to push the envelope and tell me about pursuing innovative approaches and some of the frustrations with that.

00;24;45;29 - 00;25;06;23 Dr. Winer With the way we typically think about science in the way grants are given out.

Dr. Bindra Yeah, it's our most recent work developing an analog of a drug called Temozolomide. And this was the paper we published in Science. We

saw a patient that become resistant to temozolomide and came back to my laboratory and said, We're going to make a new version of that drug.

00;25;07;05 - 00;25;25;11 Dr. Bindra Well, it turns out making a new version of a drug and not being a chemist myself is very, very difficult. And so I had to go to a wonderful lab here at Yale, Seth Herzon's lab, synthetic chemistry lab, and the two of us work together. He didn't study much cancer biology. I didn't do much chemistry, but we worked together to develop this drug.

00;25;25;24 - 00;25;50;20 Dr. Bindra Our first couple of grants were rejected. In fact, some some of the reviewers said this would never work long before we got it to work. And a lot of this about is about persistence and just not being jaded by people that say this isn't going to work.

Dr. Winer Yeah, no, I mean, I think of frustration that that sometimes people have is that in order to get funding, you have to almost have completed the work in advance.

00;25;50;20 - 00;26;18;15 Dr. Bindra And I think we continue to need to support people who are going to be innovative and take risks because that's how we're going to really move the field forward. And what I'm struck by, though, is that it's a patient you saw in clinic with resistance to temozolomide that made you want to do this. It's why I love being a physician scientist.

00;26;18;15 - 00;26;37;28 Dr. Bindra It's really an honor and a privilege to be able to work with patients because, as I said earlier, they inspire us every day. And we came back. I still remember the day I came back from that clinic and there was an MVP, 22 year old kid in our laboratory who said, Could you solve this problem? And he started drawing out the structure of the drug and said, I think I can do this, but I need a chemistry lab.

00;26;38;21 - 00;27;03;21 Dr. Bindra And we went to the chemistry lab and he was off to the races. It's just so much fun doing this type of work. Well, and of course, you know, with cuts in federal funding and with cuts related to training grants, I think one of our big fears is that those 22 year olds will get turned off from science because they feel like they're not getting supported.

00;27;04;02 - 00;27;24;25 Dr. Bindra And we desperately need not to lose a generation of people. Exactly, I tell this to patients as well as they asked, you know, is there a future? Are there going to be new drugs in five years if this drug doesn't work? And I say, thankfully, this this country and the world is committed to new research and new ideas do that.

00;27;24;25 - 00;27;58;02 Dr. Bindra We need those 22 year old kids to come out with those innovative ideas and to push the envelope altogether.

Dr. Winer No, I mean, we definitely need young brains. So with that in mind, you know, you were once a Yale College student. You were an M.D., Ph.D. student. Here. You're talking now. Imagine being a young person interested in medicine and science, what's your advice to them?

00;27;59;06 - 00;28;17;11 Dr. Bindra So my advice is, first, don't be scared of. Of course, it's a very uncertain times for us. Science has always been my true north, and it's here on the side of science will always be right, because the pursuit of knowledge is what we need to do. There will always be problems that we need to solve and questions we need to ask.

00;28;17;26 - 00;28;34;11 Dr. Bindra And health and human disease. I always tell people we're all human with regardless of what stage we are in life, how much money we have, we all need to help each other out and people always get sick. And so this is a wonderful field to think about going into because there's always going to be something to do to help our fellow humans.

00;28;34;18 - 00;28;59;07 WNPR Dr. Ranjit Bindra is a physician scientist at the Yale School of Medicine. If you have questions, the address is cancer answers at Yale that Edu and past editions of the program are available in audio and written form at Yale Cancer Center. Dot org. We hope you'll join us next time to learn more about the fight against cancer. Funding for Yale Cancer Answers is provided by Smilow Cancer Hospital.