

Support for Yale Cancer Answers comes from AstraZeneca, providing important treatment options for women living with advanced ovarian cancer. Learn more at astrazeneca-us.com. Welcome to Yale Cancer Answers with doctors Anees Chagpar and Steven Gore. I am Bruce Barber. Yale Cancer Answers features the latest information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week it is a conversation about therapeutic radiology and new research in the field with Dr. Ranjit Bindra. Dr. Bindra is an Associate Professor of Therapeutic Radiology at Yale School of Medicine. Dr. Gore is a Professor of Internal Medicine and Hematology at Yale and Director of Hematologic Malignancies at Smilow Cancer Hospital.

Gore So, therapeutic radiology as I understand, this would be like what we might call radiation oncology or radiation therapy I think we used to say in the old days?

Bindra Yeah, exactly. So, one of the classical names for our field was therapeutic radiology and in more modern times, you often hear it referred to as radiation oncology.

Gore Okay. So, but you are in an old-fashioned department, the likes you used the old names, is that right?

Bindra Exactly, exactly. We would like to keep it real.

Gore Keep it traditional.

Bindra Exactly.

Gore Right, and you really work with some of these really new toys that are ultra-focused, right?

Bindra Yeah, it is pretty remarkable. I would say over the last 10-15 years, our field has changed in many, many ways. We can now deliver ultra-precise doses to very, very small regions, delicate regions in the brain, and it is really exciting to be able to do this because we can treat tumors that previously were really thought to be untreatable.

Gore And, some people call this surgery right? Like radiation surgery or something like that? Bindra Yeah, some of our treatment involves what we call radiosurgery, which is essentially a non-invasive way of treating tumors without knives. Gore Yeah. Could you explain how that works if you could make it simple for our listening public?

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Bindra Yeah. So, often what I tell patients for instance who have a brain metastases, who are about to undergo treatment at Yale that we do called gamma knife radiosurgery, I think of it as taking a magnifying glass and shining on a leaf. To be more specific, if you can think of 200 beams – all focused on a

single point less than the head of a pen, almost, we can do that with our gamma knife radiosurgery and treat tumors that are very close to delicate structures such as the brainstem or the optic nerves.

Gore You are reminding me of the Death Star in Star Wars.

Bindra That is a pretty good example. I think that very high-tech and ultra-focused.

Gore I see. Which is kind of scary if I were a patient I suppose, but I would trust you, I would have to trust you, right?

Bindra Yeah. We find a lot of patients find the name to be very scary. When they actually see the instrument and see the team, it is not that scary at all.

Gore Does it look like a basic scanner, like a CAT scanner or...?

Bindra It sort of looks like, if you have ever been to a hair salon and someone's getting their hair dried, you will see that helmet that gets on top of...

Gore The old-fashioned lady's hairdryers with curlers?

Bindra Exactly. It sort of looks like that.

Gore So, you put that thing over their head?

Bindra We put that thing over the head and our neurosurgeon actually fixes a stereotactic frame that actually reads out the xyz coordinates with very high precision, less than a millimeter of uncertainty that allows us to treat these tumors in the brain.

Gore Wow, that is really crazy I would say. I mean, that is my response. So, the neurosurgeons, they put in this frame work that is like surgery, are there screws or something to do that?

Bindra Exactly. Its 4 pins that are affixed just to the outer table of the skull. It allows us to then take an MRI with that frame in place and that gives us the xyz coordinates and then we can simply point to where we want to treat and the machine will direct its beams to that location.

Gore But it is a little more complicated isn't it then like if you are doing a video game and you just like took your mouse and circled it and say go zap it, right?

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Bindra Exactly. There is behind the sort of front interface, there is a lot of complexities. We have a team of physicists, the radiation oncologists, the actual instrument itself has a great deal of complexity regarding the software to make sure that they can align everything perfectly.

Gore Well, that is really, you know, I did not like the idea of your technologist sitting there or you even Ranjit sitting there with a mouse and just saying okay zap.

Bindra You know me too well.

Gore Yeah, exactly. That could be a problem. Now do you treat mainly, you said metastatic cancers that would be something like a breast or lung cancer that had spread to the brain?

Bindra Yeah, so, with radiosurgery, we treat primarily brain metastases, but we also treat variety of benign tumors as well. The majority of my practice is actually focused on adult and pediatric brain tumors that are primary brain tumors. We refer to these as gliomas.

Gore Okay. And aren't those often treated with surgery?

Bindra So, day in age, these tumors are treated with a diverse range of modalities, almost all patients will get a surgery followed by postoperative radiation therapy, often combined with chemotherapy, and then followed by systemic therapies as well.

Gore So, this would be one of these multidisciplinary team kind of things?

Bindra Exactly. Again, another example of how things have really changed in the last 10 years in how we manage these tumors.

Gore So, do most people with brain cancer end up receiving several of those modalities?

Bindra I would say about 70-80% of the patients, both in the adult realm and the pediatric space as well receive this treatment.

Gore Gotcha. So, we are here to talk a little bit about research in the treatment of cancer, and I am just wondering how one laboratory, or maybe it is not like that, can model this kind of multidisciplinary stuff. I mean, you are trained as this kind of beam shooter guy, but that is not all you do in the laboratory, right?

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Bindra Yeah, that is a really great point. I think over the last 6 years that my lab has been open, I think one of the things we have realized is that the only way to make progress is to develop a team-based approach, really cross-disciplinary in nature. So, in our laboratory, we are obviously radiation based, but we interact with the medical oncologists, the neurosurgeons and actually even bio-engineers as some of our most recent work we're using nanoparticles to deliver some of our drugs directly into the brain to treat these tumors.

Gore So, do you have like little gamma knife machines for your rodents or whatever it is you are working on?

Bindra So, we always joke that we have the highest quality rodent standard of care radiation equipment in our department, so we indeed try our best to model both the radiation delivery as well as the actual tumors. So, we have

patient-derived tumors grown from patients from the OR and we use those to find the best treatments that we can for our patients.

Gore Oh wait a minute. So, you have taken the tumor out of the patient and you are growing it in a box or what are you doing?

Bindra So, we often will have a specimen from the operating room and we will take it and will put it in the brain of an animal.

Gore I see, so it is inside a living thing, it is not like sitting there like throbbing like the blob or something in a movie?

Bindra Exactly, exactly.

Gore That's a little scary.

Bindra And of course, we do it in most humane way possible and I think it is actually a very important way for us to model these treatments that we are designing for patients.

Gore So, you can grow the cells from the brain cancer of the human being inside the mouse? Or rat, I suppose.

Bindra Indeed. We do it rats and mice, and it turns out that modeling in this manner, tends to preserve the original architecture of the tumor and better models the in vivo environment in a patient.

Gore Wow. So, are these special kinds of rodents or can anything you catch do?

Bindra Yeah, we use something called nude rats and nude mice. These animals do not have an immune system, so they do not reject the specimens that we put in them.

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Gore Gotcha, and so then you can treat them like you would be treating the humans, only on a smaller scale?

Bindra That's exactly the case.

Gore Interesting. So, I know a lot about your focusing on is how to do with, how to make cancer cells die better?

Bindra I think one of the biggest focal areas in our laboratory is how do we address the therapeutic index. This is something that I think is incredibly important.

Gore Therapeutic index. What does that mean?

Bindra Oh, yeah, sorry, we get so into this that always forget we need to define this. So, the therapeutic index essentially means how do we find ways to treat the tumor while sparing the normal tissue?

Gore Minimizing side effects really?

Bindra Exactly. Now, the technology that I told you earlier, the gamma knife and all those radiosurgery technologies, they are really great at localizing our beams of energy to the tumor. We still need to find a way to separate our tumor cells from our normal cells when we actually treat them with our various therapeutics.

Gore So, how do you do that.

Bindra So, a lot of it is looking at the intrinsic tumor genetics, meaning the mutations that are found in the genome of the tumor with the idea that it is very unlikely those mutations will be found in the normal tissue.

Gore So, you find out what is different about the cancer cell and you try to capitalize on it?

Bindra Exactly. We often refer to this as exploiting a defect or targeting an Achilles heel.

Gore Well, then I guess it makes sense because although cancer cells may come from normal cells originally, clearly they are behaving differently.

Bindra Exactly, sort of what we would like to say is there is no free lunch, in a sense that for the tumor cells to acquire their characteristics to grow, they often give up other things and we find those things, then we find a way to target them.

Gore So, what is an example of something that tumor cell gave up that you might be able to exploit.

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Bindra So that is a really good segue into some of the research that we have been doing over the last year or so. So, we have made a very interesting discovery that metabolites within the cell are actually overproduced in some cancers and it appears that those cancers use that to drive tumor progression, but during the course of tumor progression, they become very bad at repairing their own DNA directly as a result of those metabolites.

Gore So, let us go to this DNA repair thing. Why would a normal cell want to repair its DNA, like why would I have mechanisms for doing that?

Bindra Yeah, that is a great question. So, something I love to talk about with the trainees in my lab and what not, if you think about it, we have billions of base pairs in the genome and often we have about 7 hours to make a perfect copy with no errors. In parallel the entire time, we have a number of toxic environmental agents that are threatening our genome and the genome really is the book of life. As such, our mammalian cells or our normal cells developed a number of very, very complex important ways to repair their DNA.

Gore I see. So what is the 7-hour timeframe here?

Bindra This 7 hour is what we often refer to as S-phase and it is the time when the genome duplicates itself prior to dividing into two.

Gore So, if the cell is dividing and some toxic chemical in its environment has damaged the code, if it were to replicate without fixing itself then the daughter cells would have some mistakes in it?

Bindra Exactly. In terms of tumor genesis, those mistakes often lead to cancer. Many believe that tumor cells leverage this instability to become cancer.

Gore So, is this something it is happening in healthy people all the time?

Bindra So, believe it or not, even sitting here, we have cosmic rays that are actually penetrating through actually the 2-3 feet of cement here above us that are actually damaging our genome as we speak.

Gore Whom do I sue about that?

Bindra Probably God.

Gore We are not into a theology program, we will leave that to Krista Tippett in terms of the metaphysics there. So, we are exposed to things every day that damage our DNA and our cells want to fix it?

Bindra Exactly. 00:12:47 into MP3: https://cdn1.medicine.yale.edu/cancer/2018-YCA-0902-Podcast-Bindra_341627_5_v1.mp3

Gore Assuming that they have some well. Well, that is really interesting. I am going to want to learn more about how you are exploiting this DNA damage and repair access if you will or system, but first we are going to take a short break for a medical minute.

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Gore Welcome back to Yale Cancer Answers. This is Dr. Steven Gore. I am joined tonight by my guest Dr. Ranjit Bindra. We are discussing the growing field of cancer research and right before the break, we were discussing this ability that cells have to fix their DNA so that they do not pass on the stakes to their children cells. And Ranjit, you were indicating to me before was that, that

cancer cells somehow exploit the system for their benefit. Can you tell us more about that?

Bindra Yeah. So, this is a story that really was informed by my clinical work treating brain tumors like gliomas. We had noticed that when we treated certain tumors in the brain that have a mutation in their gene called IDH1, which is very important for metabolism of normal cells and cancer cells, we had found that when we treated them with radiation, they were particularly sensitive as if they had a DNA repair defect.

Gore Meaning that the brain cancers that had this mutation compared to brain cancers that don't were more sensitive to radiation?

Bindra Exactly.

Gore Okay. Well, that is very interesting. I understand that this is a mutation that is not uncommon in brain cancer.

Bindra Yeah, it is about 70% of what we call lower grade gliomas, and that prompted us actually to go back to laboratory. We had a wonderful Fulbright student, medical oncologist from overseas who joined us and over about the course of a year, we decided we would model those mutations and see if we could recapitulate that sensitivity in the laboratory.

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Gore So, how do you do that? How do you model that?

Bindra So, we used something called CRISP-R cast based gene targeting, I think back in the days several years ago, it was quite novel. I think now everyone is doing it, I used to joke that my 8-year-old daughter probably will have a science project on it soon.

Gore Well, I am thinking of, you just made me think about the old chemistry sets that I used to have, you probably were too young to have them.

Bindra No, I had them.

Gore So, now you are going to have your own CRISP-R casts biology set. So, this is a way of cutting out genes or putting in genes, specifically into cells, is that right?

Bindra That is correct. It is sort of like a genome scissors and so we actually made one of the first CRISP-R cast-based models of the IDH mutation in brain tumor model cell lines that has ever been reported.

Gore So does that mean you put the gene in or you took it out or what did you do?

Bindra We actually inserted a single-base per mutation in the genome of these brain tumor cells to model the IDH mutation exactly.

Gore Okay, and you grew that tumor up in mice?

Bindra We actually did something called a drug screen where we looked at dozens and dozens of DNA repair inhibitors and asked the question where there were specific DNA repair inhibitors that were sensitizing to the cells that have the IDH-1 mutation.

Gore Okay, so let me just get this straight. So, you've got cells that have this mutation growing in some kind of petri dish or a flask and you are treating them with chemicals that you get off the shelf basically that you think have something to do with inhibiting this repair system?

Bindra Yeah, and to our surprise, we found one drug that was already FDA-approved that was highly active against the IDH mutation.

Gore So this killed those cells way better than the cells that did not have the mutation?

Bindra It was actually surprising, we had to almost re-run the experiment several times because we did not really believe it at first, and we realized that it was a consistently about 100-fold selective cell kill for cells with the mutation.

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Gore And that was without radiation or?

Bindra That was actually without the radiation.

Gore Just the chemical? Bindra Yeah, exactly.

Gore So, you are trying to put yourself out of business?

Bindra We always joke that I need to make sure I do more radiation studies, but we just follow the biology, we follow the data, and it was the chemical that was the most active.

Gore You studied the chemical with radiation?

Bindra Our thoughts are that we would like to do that in the future. We just see such exquisite sensitivity with this particular agent, we have been testing it alone, maybe in combinations in chemotherapy, but definitely radiation in the future.

Gore Interesting, but I also know that there are challenges or there can be challenges to delivering chemicals into brain tumors because the brain has a good way of screening out chemicals right?

Bindra Yeah, that is called the blood brain barrier, and we have actually found a number of drugs in this class that are sensitive against this mutation that actually have excellent CNS penetration.

Gore So, they cross the blood brain barrier?

Bindra They do, and we also have a set of drugs that don't, but we are developing new methods to deliver those drugs directly into the brain, which is really exciting.

Gore Very cool. So, I imagine that once you had this exciting chemical in your hands and you had these mice or rats that were growing these human tumors, I mean if I were you, I might have like tried that. I might have given the chemical to those rodents.

Bindra Yeah, that was the next thing we did. You know the first thing we did is actually figure out the exact mechanism.

Gore So, you should hire me I think.

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Bindra Well, we do have an empty bench in the lab. So, we figured out the mechanism of the interaction and it was related to the DNA repair defect in these cells with the IDH-1 mutation and then you are exactly right, we then tested it in animals and proved that we recapitulate it in vivo.

Gore And again, this is just the chemical and no radiation and no chemo per se.

Bindra You are correct.

Gore Okay. What is this drug FDA approved for? What are you using it for usually?

Bindra So, this drug called a PARP inhibitor and it is FDA-approved for breast and ovarian cancers that have a specific mutation in 1 of 2 genes called BRCA-1 or BRCA-2 but not IDH-1. Not IDH-1 until now and we are testing it in a clinical trial that just opened last week.

Gore So, do your brain tumors that have this IDH-1 also have mutations in these BRCA genes.

Bindra So, actually they have mutations only in IDH-1 or IDH-2 and we would argue that they are identical to BRCA-1 and BRCA-2, so they are actually mutually exclusive, those mutations.

Gore In other words, if you have one, you do not need the other one because they do the same thing?

Bindra Exactly, and that is really the core of our discovery that the IDH-1 mutations essentially are just like having a BRCA-1 or a BRCA-2 gene mutation which is very, very unexpected.

Gore So, you said that you opened a clinical trial testing this in human beings?

Bindra Yeah, this was one of the most exciting things and I really credit the collaborative environment at Yale for this, working with a phase-1 team here at

Yale, we were able to essentially take that discovery from our lab just about 12 months ago and we joined together and wrote a clinical trial and believe it or not, we will be treating our first patient in about 4 weeks.

Gore Twelve months from making this observation in the laboratory to testing a drug in humans, that is really incredibly fast in my experience.

Bindra It is very, very exciting. I think that it really highlights how the paradigm for drug development is going to change I think as academic centers like Yale and other places really pursue this bench-to-bedside development. I would like to call it as retaking control of the process and putting the investigators from the academic setting in driver seat.

Gore Well, there is a lot of great scientists also working for pharmaceutical companies, I do not think anybody has any specific license or insight, maybe you do because you are treating patients and they are not, I do not know.

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Bindra That is true. I think it is more the time to development. So, the gap between academia and pharma often can be several years and when you pursue some of these approaches, we can really leapfrog into the clinic faster.

Gore Even I think that one of the cool things is that you because you are very invested in this thing that you have discovered for very good reasons, and you get embedded by your colleagues to say it is not just Dr. Bindra's kind of crazy idea that is really looks kind of half-baked to everybody else, but once you get that validation, you can make it a prime go-forward effort, whereas if you are in a pharma company they might say well that is really interesting Ranjit, but you know we have got these other things that we are planning to do, or that we owe our shareholders just higher on the agenda right?

Bindra Yeah, no I totally agree, I mean for the record, it is still pretty crazy idea but we are moving forward with that. I think that we are very excited about this interaction.

Gore So, you are testing the actual drug that you discovered in the screen or a different drug in the same family? Bindra Yeah, so the original drug we discovered in the screen was not CNS permeable or it did not pass the blood brain barrier, so we essentially went out on a campaign to find one that was, and when we did, we called up that company and told them that we really had some compelling data that they needed to see and we asked them if they would join us on this journey to get this into patients as soon as possible. Gore And they have agreed to do that?

Bindra They have, they have. It has been a really interesting experience overall trying to get this trial off the ground. I think as I said IDH mutations are relatively common, but this discovery was very unexpected and it has taken a lot of time to get the research community on board and to believe our work.

Gore I know 1 year sounds pretty fast to me. Bindra That still could be faster in my mind. Gore I am sure, I am sure that is true. Nothing faster than like getting a mouse out of cage and doing your experiment.

Bindra It is a good point.

Gore So, you are treating patients mainly with brain cancer then?

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Bindra We are. We actually have several versions of this trial that are about open, so what is fascinating about the way precision medicine is evolving is we are almost becoming tissue agnostic, or we are understanding that well, you have tumors that look different under the microscope, but they might share a common mutation.

Gore So, tumors from different kinds of tissues that have this mutation might behave similarly.

Bindra Exactly. Well, part of our discovery was that the IDH mutation found in brain tumors, sarcomas, a disease called cholangiocarcinoma, as well as leukemias which I know you are very well aware of, the IDH mutation - all those tumor types appears to behave the same in that it renders sensitivity to these PARP inhibitors.

Gore So interesting, and so, on your clinical trial, patients with any of those diseases or at least the solid tumors I guess that have the IDH mutations can go on?

Bindra Exactly. We call this a basket trial, in which we are driven really by the genomics rather than the histology or what it looks like under the microscope.

Gore And are these patients who have recently been diagnosed or these patients who have already had treatments that have failed to work or stopped working?

Bindra Yeah, so typically we focus on the recurrent patients that is often a standard way when you have a very experimental therapy. It was interesting, as we designed this trial, a lot of people asked, well you know when you slice and dice these different tumor types, there is going to be subgroups upon subgroups and they asked us how are you actually going to accrue to the study, how are you going to get the patients to run the study in an efficient and feasible manner.

Gore And what is the answer to that?

Bindra The answer is something that really surprised me. It is the power of social media and the extent to which the average patient is really plugged in to the research community, a level that is unparallel to what has been seen previously.

Gore Always the average affluent, highly-educated patients are motivated. Bindra You would be surprised, friends of friends, you know I have gotten part

of the chondrosarcoma support group on Facebook, and actually get posts that call me out people from rural counties in Virginia as a friend of friend that heard about a trial, and I find it very, very exciting and it is almost like the patient is empowered to a whole new level.

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Gore It is actually quite interesting because I think the difficult side for me is that the patients or family members will hear about something that is written in The New York Times or another newspaper that has no relevance to their disease, but it is cancer and so they want to know about that, which is fine, it is good that people pay attention but it is obviously even better if they can pay attention to the stuff that's somewhere in the same ballpark right?

Bindra No, no I agree, but I think in parallel what we are seeing is if you go on Twitter and anyone out there should follow me on Twitter: @Ranjit.Bindra, we see that the patient advocates are all on Twitter now and it is neat because you will see them re-tweeting stuff, you will see them translating things. I actually got reached out to by patient advocate group that said "well, we read your tweet and can you give us a layperson version of it" and more re-tweeted. That was really interesting because we are thinking about things completely differently than we used, you know just 5 or 10 years ago in the clinic.

Gore It is interesting. I do not do Twitter myself, but I can see how things like Twitter could be very powerful and really wonderful resources for these patient groups to try to aggregate data, that the patients otherwise would not have access to and their physicians probably do not either.

Bindra I totally agree 100%.

Gore I would imagine that since this drug is FDA approved, was it never studied in brain cancer before?

Bindra So, it's a great question. It turns out that the PARP inhibitors were tested in a lot of gliomas, but believe it or not, they actually excluded the patients with the IDH mutation.

Gore Why would they do that?

Bindra Because it turns out that the IDH mutant patients as I mentioned earlier respond better to radiation, it is not a durable response, it does come back.

Gore So, they were thought to be too good a cancer, in other words there was already good therapy for them?

Bindra Exactly, which sort of confound the statistics by creating a heterogeneous group of responses, and so they actually excluded those patients and we actually had to fight pretty hard to launch this trial because a lot of people said, well PARP inhibitors have already been tested in glioma and they do not work and

we said, well actually if you look at the eligibility criteria, all the patients that would have responded were actually excluded.

Gore It is a very serendipitous set of circumstances there really.

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Bindra It is really fascinating. What I love about science again and you know following the biology and just seeing where it takes you, you will always be surprised.

Dr. Ranjit Bindra is Associate Professor of Therapeutic Radiology at Yale School of Medicine. If you have questions, the address is canceranswers@yale.edu, and past editions of the program are available in audio and written form at YaleCancerCenter.org. I am Bruce Barber reminding you to tune in each week to learn more about the fight against cancer here on Connecticut Public Radio.