Yale CANCER CENTER answers

WNPR Connecticut Public Radio

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Pediatric Tumors and the role of Therapeutic Radiology

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Yale Cancer Center Answers
is a weekly broadcast on
WNPR Connecticut Public Radio
Sunday Evenings at 6:00 PM

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Welcome to Yale Cancer Center Answers with doctors Francine Foss and Anees Chagpar. Dr. Foss is a Professor of Medical Oncology and Dermatology, specializing in the treatment of lymphomas and Dr. Chagpar is Associate Professor of Surgical Oncology and she is a Director of the Breast Center at Smilow Cancer Hospital at Yale-New Haven. If you would like to join the conversation, you can contact the doctors directly. The address is canceranswers@yale.edu and the phone number is 1-888-234-4YCC. This week Dr. Anees Chagpar is joined by Dr. Ranjit Bindra for a conversation about the research and treatment of brain tumors. Dr. Bindra is Assistant Professor of Therapeutic Radiology and of Pathology and Assistant Professor of Therapeutic Radiology at Yale School of Medicine. Here is Dr. Chagpar.

Chagpar Why don't you start off Ranjit by telling us a little bit about what you do and what therapeutic radiology is all about?

Bindra I am Assistant Professor here at Yale, as you mentioned, and I split my time between the lab and the clinic. In the clinic I treat adult and pediatric brain tumors, primary high grade tumors often referred to as glioblastomas. In the laboratory I do similar work, translate some of the work that we do in the clinic into the research setting and my lab is composed of about 8 people. I have some students, graduate students, medical students, undergrads, a post doc and a lab manager and our main focus is developing novel drugs to combine with radiation therapy specifically for these brain tumors.

Chagpar Let's start by setting the stage clinically in reference to brain tumors. You said that you treat primarily brain tumors, especially glioblastoma, can you put that in context, how common are these? How does somebody know if they are sitting listening to Yale Cancer Center Answers and wondering about their headache if they have a glioblastoma? Tell us a little bit more about brain tumors.

Bindra Certainly, the good news is that brain tumors are relatively rare, the malignant brain tumors that we deal with clinically here at Yale are glioblastomas and they affect only in the range of 10, 000 to 12,000 people per year in the United States. Typically, when you have a headache at home and I know that feeling of, this could be a brain tumor, luckily it is more likely to be just a headache, certainly you should seek medical attention if it persists for a long time, but in terms of brain tumors, this types of brain tumor, they are a very unique entity because they are highly resistant to therapy. You can cut these tumors out in the operating room and you can give lots of radiation therapy and we will talk about what that means in a moment, combining with chemotherapy and unfortunately these brain tumors tend to recur locally and that is the clinical enigma that has driven a lot of scientists and clinicians like myself to try to find better therapies for these tumors.

Chagpar What causes them and how are they diagnosed?

Bindra Interestingly with many, many years of research we are still just beginning to understand what a brain tumor is, what a malignant brain tumor is, and what the genetic events are that cause these

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tumors. We still are far away from understanding the exact sequence of events for these types of brain tumors. In terms of symptoms, as I mentioned earlier, it is more than just a headache. For example I can tell about the patient that I treated several months ago. The patient was working in his garden one day and all of the sudden had a seizure and was unconscious for quite some time and his wife found him there in the garden and low and behold they took him in the emergency room and they did a CAT scan of the brain and unfortunately this patient happened to have a malignant brain tumor which is just the beginning of the journey for that patient. So typically there is much more of a dramatic event that occurs for patients with brain tumors and often seizures are the most common presenting features.

Chagpar Was there anything that caused this? He was out in his garden like many of us would be and this just all of a sudden happened? Is this something that is genetic, is there a family history, did he eat something that was not the right thing or was he a smoker and you are not supposed to smoke? Are things that make brain tumors happen?

Bindra That is a great question and it is funny because those were the exact questions that we are confronted with in the clinic when we talk to family members and patients when they are first diagnosed, one question is, did I eat something? Is there something that I did that caused the tumor? Unfortunately, for many of these patients, much like winning the lottery, it is just a sequence of events that was unfortunate timing for that patient and something I tell my students in the lab is, we always forget this, but the human genome inside of each cell is composed of over 3 billion bases and every day many of our cells actually have to a make a perfect copy of those 3 billion bases and often they do this within hours, and as you can imagine every now and then there is a mistake that is made in the genome and what we believe brain tumors are is that there are a certain number of these mistakes that occur over time and within years those mistakes accumulate into a malignant tumor and it is often just a single cell that acquires those mutations. The short answer is that it is really often a case of bad luck and just a combination of spontaneous mutations that cause these tumors.

Chagpar So one of his cells made a mistake and he ended up with the seizure and a brain tumor?

Bindra Exactly, unfortunately that would be the short answer to that question.

Chagpar I guess that then brings us to, how it is that genes replicate, how is it that they maintain that integrity, how do we make sure that they spell check so that they do not make mistakes and so that people do not end up with brain tumors?

Bindra That is an excellent question and that is actually a large focus of my lab and many others in this field. I think it is fascinating to step back and think about first the scale of things, of Mother Nature so to speak. A single cell is about 1000 times smaller than the head of a pen and within

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that cell is a very small structure called a nucleus. In that nucleus are 3 billion bases all spread amongst a small number of chromosomes and we get half of our chromosomes from mom and half of our chromosomes from dad, and our cells have devised ingenious mechanisms literally to scan across the entire genome looking for errors, they can detect a single base pair that is a mismatch so if we have a string there are four bases A, T, G and C and that code comprises life and you can often have a string of Ts in certain areas of the genome and just as if you were to be typing at a typewriter you could see that string of T's and maybe put an extra one in and actually that happens commonly in cells and a single mismatch can have devastating consequences if there is a gene that is in that area and that gene becomes what we call frame shifted and everything gets out of whack for that gene and it becomes non-functional, so the cells devise numerous mechanisms within seconds to recognize that damage, that mismatch, and you can actually look at one strand that freshly made over the older strand based on a series of marks that are placed in the surrounding genome and you can use that to repair that damage.

Chagpar So your body has figured out ways of spell checking, of figuring out where these mistakes are and fixing them. So that cannot be failsafe because otherwise nobody would ever have mistakes made and this patient would not have had a seizure in the garden?

Bindra Exactly and the interesting thing about ourselves is that there are backup systems upon backup systems but I was actually just in New York City this weekend at a concert and we were in Time Square and I was remarking to my wife how incredibly busy and crazy that area of New York is and actually it is a good analogy for the cell because when you look down inside a cell in the nucleus there are these mitochondria, the engines of the cell and they are generating massive amounts of energy and heat and all sorts of products that are essentially attacking the DNA. Their enzymes are constantly stitching together millions of proteins every day and often those enzymes can mistake DNA for their target and they can actually damage the DNA. Another interesting thing is the DNA itself actually gets tangled like headphone cables you have in your iPhone, the DNA actually gets tangled up and the cell needs to constantly find a way to untangle those and does that by making breaks in the DNA and then untangling those pieces. Now you can imagine if we have 3 billion bases that are constantly being attacked and tangled it would only take one mistake for the cell for that day to create a mistake that cannot be erased from the genome in that cell, so I think you are correct, the failsafe mechanisms are essential but they are like anything else, they are not perfect.

Chagpar And so in your lab, what are you trying to figure out?

Bindra We are trying to figure out when a piece of DNA is broken, exactly how it gets stitched back together. As many of you know, we have two strands of DNA, so DNA is double stranded and one of the hardest pieces of damage to repair for a cell is a double strand break. If you have a single strand break, it turns out that the cell can look at the other piece of DNA and say, well, this

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is the correct sequence and I will just use that as a copy. With the double strand break, when the DNA repair policeman arrives at that scene, if you will, they actually look at that area and they do not know what is missing from in between. They look at that double strand break and it actually takes quite a lot of thought for this cell to decide if it wants to simply just glue those two pieces together, because what if a thousand bases were missing and one was a tumor suppressor gene. So our lab tries to understand exactly what the processes are that are involved in recognizing that strand break and then how it chooses to repair that lesion. There are actually multiple ways to do that.

Chagpar How does that then help us in terms of really pushing the field forward when we think about that patient who was in the garden, who had the seizure, who ended up in your clinic with glioblastoma?

Bindra I think your question highlights the value of translational medicine because there is a link from that double strand break to that patient in the garden and the link is when we see that patient we treat them with radiation therapy and later in the session if we have time we will talk more about that treatment, but we give them very, very high doses of focal radiation directly at that tumor where thousands and thousands of tumors cells are sitting and what that radiation does is it actually induces double strand breaks in those tumor cells to prevent them from growing and they eventually die. Remarkably, these brain tumor cells are really, really good at bringing those strands back together and repairing that damage and for reasons that we still do not understand, they are able to recognize that damage faster and they are able to repair it faster and as a result, within months these tumors come back and that is why to date we have had great difficulty trying to cure tumors like glioblastoma.

Chagpar What is interesting to me is that it is the mechanism that causes these tumors to occur. The mistake in the genes that causes the patient to get the glioblastoma in the first place, but then once they have the tumor, you use the same type of idea to break the DNA to kill it. But it seems like the tumor cells have kind of got us beat because they know how to fix it more than we do.

Bindra Exactly, and that is one of the focal points of our lab, because our approach to the tumor cells is that you may have a work around but that historically we have been able to come up with a better work around and so what we actually do is we use high-throughput drugs screening to try to find compounds in novel drugs that when we hit those tumor cells with radiation, we can treat them with drug that prevents those tumor cells from repairing those breaks.

Chagpar We are going to talk more about how all of these drugs and radiation work together to fix DNA when we come back after this medical minute. Please stay tuned to learn more information about therapeutic radiology and more about these double-strand breaks and DNA repair that has a lot to do with glioblastoma with our guest Dr. Ranjit Bindra.

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Medical Minute *Breast cancer is the most common cancer in women. In Connecticut alone approximately 3000 women will be diagnosed with breast cancer this year, but there is new hope. Earlier detection, non-invasive treatments, and novel therapies provide more options for patients to fight breast cancer. Women should schedule a baseline mammogram beginning at age 40 or earlier if they have risk factors associated with the disease. With screening, early detection and a healthy lifestyle, breast cancer can be defeated. Clinical trials are currently underway at federally designated comprehensive cancer centers such as Yale Cancer Center to make innovative new treatments available to patients. A potential breakthrough in treating chemotherapy resistant breast cancer is now being studied at Yale combining BSI-101, a PARP inhibitor with the chemotherapy drug irinotecan. This has been a medical minute brought to you as a public service by the Yale Cancer Center. More information is available at yalecancercenter.org. You are listening to the WNPR Connecticut's Public Radio-station.*

Chagpar Welcome back to Yale Cancer Center Answers. This is Dr. Anees Chagpar and I am joined today by my guest Dr. Ranjit Bindra. We are talking about therapeutic radiology, or radiation oncology and specifically radiation oncology for brain tumors and right before the break Ranjit you were telling me about high throughput drug screens that you do that are really helping to figure out how cancers can work in terms of double-strand breaks and so on. Can you tell us a bit more about that?

Bindra High-throughput drug screening is an enormously powerful way to discover new cancer therapies and therapies for other diseases. My lab generally uses high throughput drug screening to find novel anticancer drugs and we try to target the specific mutations associated with brain tumors. High-throughput screening itself is generally comprised of large drug libraries, hundreds of thousands of unique molecules and we try to sift through those molecules to try to find a compound that will specifically affect our cancer cells in the way that we want them to. For instance, if you wanted to look at a way to selectively kill a glioblastoma tumor cell with a specific mutation, you could screen two hundred thousand compounds and try to find a drug that specifically just kills those cells and has no affect on normal cells.

Chagpar Is this kind of like what people talk about when they talk about personalized medicine?

Bindra It is in many different ways. In personalized medicine the endpoint is the recognition that every tumor and every disease has a specific set of mutations that may be unique from another individual's tumor, and that is an important feature because even back when I was a med student in the early 2000's, we would look under the microscope at a brain tumor for instance and we just called it a glioblastoma and there were four or five features, the size of the nucleus, the amount of cell death, and that would label it as a glioblastoma under the microscope. We now understand

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that there are multiple different molecular subtypes with all unique different gene expression patterns. Such that in the era of personalized medicine or therapies we will have to be more targeted specifically to the gene expression changes associated with that subtype of the tumor.

Chagpar When you are doing these high-throughput-drugs screens, are you taking an individual's brain tumor and screening all of these thousands of drugs to see which drug would be best for that particular patient?

Bindra Yes, in essence we are. What we do is we have cell line models where we take the mutation that was found in a specific patient and then express it in a model system. Because we want to clear out all the noise associated with other genetic changes in that individual and ask the question, does this brain tumor harbor this gene mutation and we would like to find a drug that targets that gene mutation and in the old days when there used to be a very small number of drugs available for patients, this is in the 50s and 60s, it was a different story, because there was really nothing more we could offer them, but now we know that there are hundreds of thousands of drugs out there yet to be discovered that we can use specifically to target that gene mutation.

Chagpar This patient, who was in his garden and had a seizure and came in with the glioblastoma, does every patient now have a biopsy done of their brain tumor and are genomically profiled and because you identify a mutation in point X, you now know that drug Y is the right drug to treat that patient?

Bindra That is exactly where we need to be and my best answer to that is that are almost there and I am incredibly thankful for cancer research funding in this day in age. We all know it is difficult with the funding climate but because of that funding we have now gotten to that position and again I remark that I trained here as a medical student at Yale and even in the last 10 years coming back on faculty it has completely changed and now we know these gene mutations and we're just beginning to start the clinical trials to do exactly what you said, if this patient has a gene mutation here, and let's come up with a tailored therapy. So my guess would be that in the next 5 to 10 years this will become almost a common practice for brain tumors.

Chagpar That is fantastic. At the beginning of this show you said that you do not just treat adults, you treat kids too. So do kids get brain tumors?

Bindra Yes, unfortunately, but thankfully it is rare that kids get brain tumors. Also unfortunate is that children get these same highly aggressive tumors, namely glioblastoma, and another tumor called a brain stem glioma. There are a number of other cancer types in children such as leukemia and lymphoma but pediatric brain tumors are an interesting entity because it is really only in the last two to three years that we have come to understand that these brain tumors, although they look identical under the microscope, are completely different. Unfortunately in the previous years we

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used to just take adult experimental therapies for brain tumors and apply them to children and now we are understanding through the last 3 to 4 years of research that these are actually unique tumors and need to have their own therapies developed for them.

Chagpar So pediatric brain tumors are entirely different from adult brain tumors?

Bindra It was completely surprising and there is a string of papers in the last two years that have come out saying again that they look exactly the same under the microscope and the mutations that are common in adults are actually rare in children and there is a new set of mutations, mutations that actually affect the way that the genome curls around itself. So these are called mutations in chromatin-modifying genes. We are finding these mutations that we never even knew possible only in pediatric brain tumors, which is fascinating and makes us realize that we are just beginning to understand where we can go therapeutically with those tumors.

Chagpar And hence finding those mutations and knowing which mutations are which is really helpful.

Bindra Yes, exactly I think that is the case.

Chagpar When kids present with brain tumors is it the same set of symptoms that adults present with, such as seizures?

Bindra Kids present with very similar findings, but I tell my resident, isn't it funny how the workup and management of a child with a brain tumor is very similar, yet the entire context is different. Oftentimes they are at daycare and they start acting a little bit odd and different from what they usually do and it is much harder with children and I have a 3-1/2 year old that is quite quirky and sometimes does things you would not expect, and unfortunately that often draws out the diagnosis for children. But I think one of the biggest struggles with children with brain tumors is that it becomes an all-encompassing event, that entire family comes to your clinic and the mom and dad are devastated and confused and rightly so because they were not expecting their beautiful young child to now have this brain tumor.

Chagpar I can imagine that not only is it devastating when you get the diagnosis, but I am still struggling with how do they get there? I am certain that there are people who are listening to us, who are thinking, I have a kid. My kid goes to daycare. They act out all the time, does my kid have a brain tumor? Can you give us an example of what might be an event or something that makes people take their kids to the doctor. I mean if you have a seizure and you end up unconscious in your garden, I get it, you have to go to the hospital, but how are pediatric brain cancers diagnosed?

Bindra I trained at Sloan-Kettering during my residency and I still remember the first patient, the first child that I treated as a resident and that inspired me to go into pediatrics and she had a brain stem

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glioma and it was picked up because she had slurred speech and it was persistent and one side of her face started drooping. Often those are very clear telltale signs. I still remember the look on her face and her parents when the right side of her face started drooping and it was clear pretty quickly in that case that she had a brain tumor and she ultimately was found to have something called a brain stem glioma where the entire brain stem gets replaced by a high grade tumor.

Chagpar One of the things that is so difficult in what we do is helping people through the diagnosis of cancer, and one of the things that I love about what I do as a breast cancer surgeon is I get to tell people, Congratulations! They may have cancer now, but in the day or the week it will take to get to the operating room, we will take out that cancer, they will be cancer free and their outcome is going to be fantastic and they are going to live a long and healthy life. It is different with kids and particularly kids who have high grade brain tumors, tell us about that.

Bindra I think it is an excellent point. It is something that we struggle with almost every day. I think one of the hardest things that I have had to learn as a new attending here at Yale is breaking news and breaking news in the context of too some degree that there may be no hope. What I do tell my patient's now is that times are changing and just around the corner we are not sure when a new therapy that will be available. One of the biggest challenges is speaking to a family and I have been trying to explain to them that their child has an 80% chance of not surviving past five years and I just had a conversation with a family last week about this patient that had a high grade glioma and I think one of the most fascinating things for me is when you look at that child often the child has no concept and no idea of what is happening to them and to some degree it makes it more bearable to see that child because they are so happy. I told my residents, we as a society have a responsibility to take care of our children because they are helpless and they are depending on us and so as doctors that is just as important, we have to take care of these kids with brain tumors and as a result seeing these kids succumb to their tumors, it drives me, it drives my lifestyle. It drives all of us here at this hospital because at the end of the day what parents do not want to hear is that there is no hope, and so what we try to do is say, we are in the lab, we are working on this. And sometimes we can be frank with them and say, it may not be for your child, but I want you to know that your child is inspiring us to work. Recently, I was just awarded a grant from a small foundation and I was able to speak with the founders later and it turns out that they actually had known about the same child who died of a brain stem glioma and they had interacted with that family and I realized it was actually the patient at Sloan-Kettering that I told you about. Through them I was able to send a message to them and I said, I just want you all to know that I have received this grant from this foundation and a lot of it stems from my interaction with your daughter who passed away at about 3 years old and they sent a message back through the foundation, so it was relatively anonymous and they said, this means the world to us that our daughter is not forgotten. So I think to some degree it is frustrating. We walk out of the Tumor Boards and sometimes you say, everyone is dying, this can't be fixed, but then you start to realize

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that eventually through enough ingenuity and people all working together at institutions like here and elsewhere that we will find a cure for this disease, it is really just a matter of time.

Dr. Ranjit Bindra is Assistant Professor of Therapeutic Radiology and of Pathology and Assistant Professor of Therapeutic Radiology at Yale School of Medicine. If you have questions or comments we invite you to visit yalecancercenter.org where you can also get the podcast and find written transcripts of previously broadcasted episodes. You are listening to the WNPR Connecticut Public Media Source for news and ideas.