

Yale CANCER CENTER *answers*

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Hosts

Anees Chagpar MD

*Associate Professor of
Surgical Oncology*

Susan Higgins MD

*Professor of Therapeutic
Radiology, Obstetrics,
Gynecology, and
Reproductive Sciences*

Steven Gore MD

*Director of Hematologic
Malignancies*

Cancer Biology and Therapeutics

Guest Expert: Ranjit Bindra, MD, PhD

*Assistant Professor of Therapeutic Radiology and of
Pathology, Yale School of Medicine*

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Welcome to Yale Cancer Center Answers with your hosts doctors Anees Chagpar, Susan Higgins and Steven Gore. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital. Dr. Higgins is Professor of Therapeutic Radiology and of Obstetrics, Gynecology and Reproductive Sciences and Dr. Gore is Director of Hematological Malignancies at Smilow and an expert in Myelodysplastic Syndromes. Yale Cancer Center Answers features weekly conversations about the research, diagnosis and treatment of cancer and if you would like to join in, you can e-mail your questions and comments to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC. This week it is a conversation about cancer biology and therapeutics with Dr. Ranjit Bindra. Dr. Bindra is Assistant Professor of Therapeutic Radiology and of Pathology. Here is Dr. Susan Higgins.

Higgins I thought we would talk about radiation oncologists and how they play a role in the whole management team that takes care of brain tumors at our institution.

Bindra I am happy to do that, radiation oncology here at Yale is part of a multidisciplinary team. We work with surgeons and medical oncologists and we all have our own part of the puzzle that we contribute to. We deliver focused radiation which typically is given over a period of four to six weeks or so and after that we will typically hand off our treatment to our medical oncologists who will then give chemotherapy for often a period of 6 to 12 months. All this pretty much starts with a surgical resection which is done by our neurosurgeon on the team.

Higgins And then after you have this initial surgical procedure, the whole team gets together at a thing called a Tumor Board. I think a lot of patients that come to us do not realize that after their initial meeting, let's say with you, there is a whole group of doctors that come up with a game plan and as a multidisciplinary team member in GYN Oncology, I think CNS tumors like brain tumors are one of the most important tumors to get it right the first time, you have to have a game plan. Maybe you could talk about the game plan process and Tumor Board.

Bindra That is probably one of the most exciting parts of the process and I think one of the strengths of an institution like Yale, that we get a large group of people together every week and we talk about the cases that are new diagnosis, the cases that might be coming up, the cases that unfortunately have had recurrence or needed additional treatment and what is really nice about that is, you are getting a bunch of people into a room and looking at all the data, all at once and thinking about things and we often start this off with a case presentation, the resident that is on the service who is a doctor in training will present a particular case. We will then have the radiologist come and present the imaging findings and we will all look at those imaging findings together and come up with our interpretation and then immediately after we have a pathologist who comes on board and looks at the actual microscopic slides and looks at the tissue specimen and says, well this is the diagnosis that I think it is and then the consultants such as the radiation oncologists and the medical oncologists, or technically the neuro-oncologists, then all come

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together with the surgeon and we discuss what is the most optimal treatment regimen that we should give for this particular patient, recognizing that there is never always the exact answer that you pull out of a book. It often comes from a consensus.

Higgins I really like your point about the fact that there is really no replacement for everyone being in one place at one time in the process of discussing the case with the pathologist. You have the screen in front of you, you can ask them specific questions and you get the discussion plus the help of all these other specialists that are part of the team, and I do not even know that sometimes people know that they are part of the team but it is a real group effort and in talking about it I just wanted to go a little bit into this tumor board issue again in more detail because there are two types of tumor board now; for the patients with brain tumors, there is one tumor board where I understand you discuss the primary tumors, and now there is a whole separate tumor board for metastatic disease, maybe you could tell us about that.

Bindra I have this similar conversation with my patients in my clinic quite often where they say, who do you have to talk to now and I would say, well we actually have a separate tumor board just to talk about this specific part of the treatment plan and a lot of people are surprised to hear how specialized medicine becomes and the analogy for folks that are listening that might not have a medical background is, if you need to see a lawyer, there are real estate lawyers, there are tax lawyers, there are property lawyers, everything has become so specialized and just in that manner cancer care has become pretty specialized and even within the brain we have tumors that arise from the tissues within the brain or tumors that arise from other sites outside of the brain and those we call metastases or metastatic tumors and because there are such specific treatment regimens we give for those two types of tumors, we actually have an entirely different tumor board where we just talk about the management of metastatic disease.

Higgins And I think that this area of treating metastatic disease is really a new frontier in the sense that we have so many things available that were not available before. We have a tremendous impact because now a lot of people have what we call extracranial, or disease outside of their head, well controlled, and one of their main symptoms may come from the disease that is hiding in the brain and one of the tools we have that is really exciting and great from a technical standpoint is the gamma knife. Maybe you could tell us a little bit about the gamma knife because we actually have the only gamma knife in the State and you have a huge program.

Bindra I would be happy to. I think to start, one of the most interesting things about this is we are now in an era where when a patient presents with metastatic disease in the brain, it is completely different in terms of what we can do. We can say that in a large number of these cases, we can successfully address the disease in the brain and we often say, it is up to your medical oncologist to take care of the rest because believe it or not, if you have 5 or 6 small metastases in the brain, we can take care of that and a lot of that is largely due to technologies like the gamma knife radiosurgery instrument that we have here at Yale

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that is led by Dr. Veronica Chiang who has been doing this for well over 10 or almost 15 years now and we have been at the forefront in this, this concept of being very aggressive in terms of treatment of metastatic disease in the brain and we have now shown that we can easily control 5 or 6 tumors that appear and many years later, two or three might appear again and we are able to treat all of those. The important distinction is that in the past we would simply just radiate the entire brain. In a lot of smaller centers that do not have this instrument, we will rely on this backup approach where you simply just radiate the entire brain and all the normal tissue that is there, so this is a big strength at our institution and we are very excited to have it.

Higgins When people hear the word gamma knife, I think people are initially taken aback and say, what the heck is that, it sounds intimidating, but I was part of the gamma knife team for a while and it was really refreshing to see how well people tolerate it and maybe you could tell us what happens from the day a person sees you in consultation to the point where they actually get to the gamma knife center. How do they manage or tolerate that type of treatment?

Bindra Typically these patients are referred from their medical oncologist and maybe one or two spots show up in the brain and they come to our clinic and one of the 3 or 4 radiation oncologists will see them. We will do a consultation and what is really great about our program is our neurosurgery team is pretty involved from the beginning in terms of seeing these patients at the same time as us and this has actually been quite a good experience for patients, to see the radiation oncologist and the neurosurgeon sitting there in the consultation room and walk you through the procedure, getting ready for the actual day of the gamma knife, the gamma knife actual procedure, we typically say it is an all-day event for the patient. Patients will typically come in around 7 or 8 am and we check them in and we give them some medicine to relax them and then our neurosurgeon affixes the head frame which is probably the hardest part of the procedure, but only a few minutes, fixing a rigid head frame that allows us to direct our radiation beams to very high precision and we are talking about less than a millimeter accuracy. We then put that head frame on and the patient has an MRI of the brain, so we get a high-resolution image of the patient's tumors, where they are located. The patient then comes downstairs and we work with the physicist side-by-side and we delineate all the areas that are of concern and then we bring the patient into the gamma knife instrument, treat them and in many cases if it is only 2 or 3 lesions, we can treat the patient in about 20 or 30 minutes, take the head frame off and we send them home. I have a great story of a patient that called me literally the next day from the golf course telling me that he felt really good and I think that highlights how things have really changed and how we can efficiently and effectively treat these tumors.

Higgins Yeah, that also impressed me when I would see people. The frame is an open frame and I would see people sitting there drinking orange juice, waiting for their treatment and as you said, they go home and

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have very few side effects from this treatment, so a huge change from when we were all doing whole brain with people losing their hair and having lots of long-term and short-term side effects. I think we have really turned the corner in how we manage CNS disease.

Bindra And I think at Yale we have been pushing the envelope and it is partly from this program that has been built like with Dr. Chiang and having one of the only gamma knife in the State and doing about 300 to 400 cases a year which I think there is something to be said about expertise in being really at that forefront, so it has been very exciting.

Higgins And then once they go through the procedure, it is not like we just send them off into the wilderness, we have a whole process of following people, we have excellent colleagues in imaging that help us make sure that our job, if it is not done, that we finish up with that and sometimes people have additional lesions as you said, could you talk about the follow-up and how we keep people within our grasp and get them the imaging that they need as time goes on.

Bindra That is actually the great part about the Mets tumor board, because not only do we talk about patients that are on deck for treatment but we look at responses and we are really blessed to have some radiologists, Frank Minja and colleagues who have taken an interest in trying to interpret a lot of these imaging findings because we now have technology that allows us to not just look at the spot that we see, but actually look at the metabolic features within that spot just from an image that we see of the patient's brain and because of that tumor board, we are able to continuously monitor the patients and one of the other things about the gamma knife program is we are able to take new follow up scans and merge them back into the previous treatment plans so when we devise that treatment plan the day out, we can then merge those and actually look exactly where the new spot may be, and maybe sometimes we find it is actually in the same spot and we realize that this could just be a treatment change and we are just going to ride out the storm and it may resolve on its own and in many cases it does.

Higgins I think it is important to note that these are highly specialized imaging techniques, it is just not specialized treatment but the team that does the imaging and works with us really help us to make our treatment more effective and less morbid and again, being a large center with large volume and a big imaging department where they are subspecialized, has really helped us and I think they have been a big part of the team, so it is good to hear that you guys are still pushing the forefront even with the imaging and one of the things that was also interesting is the gamma knife is also used to treat some benign disease, but with really great effects. One of the things I think about is trigeminal neuralgia and maybe you could give us an update on where we are at with some of those disease processes.

Bindra We have a very busy benign disease program on the gamma knife. We actually treat a lot of trigeminal neuralgias, a lot of people fly in from all over New England and one of the great things that we have here

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is we have some functional neurosurgeons who have trained at large volume institutions that have come here and have again pushed the envelope on what we can do with non-tumor diseases and non-tumor issues. We have functional neurosurgery combined with advanced imaging and we are able to not only treat things like trigeminal neuralgia which is a benign disease that affects the nerves in the base of the skull, but we can actually retreat patients who fail, so we have a lot of flexibility and a lot of new areas that we are constantly moving towards.

Higgins I remember it was really gratifying because when I treated people with trigeminal neuralgia, getting them off of the meds that they were on and getting their functional quality of life in order meant a huge amount to them, so I am glad to hear that we are still continuing that. We are about to take a break for a medical minute, please stand by and tune in to learn more about our cancer biology and therapeutics program with Dr. Ranjit Bindra. We will be back to talk about some specific research interests and clinical trials.

*Medical
Minute*

The American Cancer Society estimates that there will be 75,000 new cases of melanoma in the US this year with over a 1000 of these patients living in Connecticut. While melanoma accounts for only about 4% of skin cancer cases, it causes the most skin cancer deaths. Early detection is the key and when detected early, melanoma is easily treated and highly curable. Clinical trials are currently underway at federally designated comprehensive cancer centers, such as Yale Cancer Center and Smilow Cancer Hospital at Yale-New Haven to test innovative new treatments for melanoma. The goal of the specialized programs of research excellence (SPORE) in skin cancer grant is to better understand the biology of skin cancer with a focus on discovering targets that will lead to improve the diagnosis and treatment. This has been a medical minute brought to you as a public service by Yale Cancer Center and Smilow Cancer Hospital at Yale-New Haven. More information is available at yalecancercenter.org. You are listening to WNPR, Connecticut's Public Media Source for news and ideas.

Higgins Welcome back to Yale Cancer Center Answers. This is Dr. Susan Higgins and I am here tonight with my guest Dr. Ranjit Bindra and we are talking about cancer biology and therapeutics and the treatment of central nervous system tumors. Dr. Bindra, one of the things that is unique about your situation is that you are an MD/PhD and you not only have the clinical expertise but you are able to bridge this gap between the science and the treatment, and we use the term bench-to-bedside projects. Could you talk a little bit about how you are bridging the gap between the clinical and science with your work in the lab.

Bindra Sure, I would be happy to do that. My laboratory is predominantly focused on small molecular screen for novel agents that we could combine with radiation and conventional chemotherapies, so what we do is we design novel assays or ways to screen large compound libraries and large collections of drugs and we

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look for specific drugs that when we give them with radiation, predominantly for brain tumors, adult and pediatric brain tumors, they are able to sensitize the effect of the radiation or the chemotherapy that is given with it.

Higgins In other words, you are effecting what we call sort of the therapeutic ratio, increasing the number of tumor cells that are killed relative to the number of normal cells that may be damaged.

Bindra Exactly and I think the key thing that you mentioned is that therapeutic index. What we tell a lot of people who are in training is that we now have instruments like we talked about in the first half like the gamma knife where we can deliver enormous doses of radiation, we can give very high doses of chemotherapy, yet a lot of these brain tumors still recur, they recur at the same site that we treated and so we need to find ways to specifically target those tumor cells without collateral damage to the normal tissue. A lot of that is now changing and that is what is so exciting to be in molecular biology, in cancer research, because we now understand the molecular features of the tumor so that we can now target them more effectively.

Higgins And you are probably involved in some clinical trials of these types of drugs, can you tell us a little bit about the trials that you are involved in?

Bindra One of our first screens that we did was looking for drugs that block DNA repair and so we are looking at DNA repair inhibitors specifically that work against a primary brain tumor called glioblastoma. We performed that screen and this was actually the work that I had started during my postdoctoral work in New York and brought over here to my own laboratory at Yale and we were very lucky because we found a drug that was previously FDA approved. It was approved for hypertension and one of the first things we were able to do was look into whether we could take that drug, since it has been given to patients for many years before, use it with radiation as a sensitizer for radiation and long story short, after about a year or two of trying to put a lot of different things together to make this work, we were able to start a clinical trial, a phase I trial which has been open for about a year.

Higgins Let's go through that process, so a patient comes to you and you have this ability to offer them the trial but there is a process that happens when they come to you in terms of consent and you have to have a long discussion about these things and educate the patient, right?

Bindra The process of enrolling in a clinical trial, from what I have noticed can be very scary for patients. They come in and we say, we have got this novel drug and I have often heard, well what is in it for you, there is a lot of fear that a clinical trial is just working maybe for a pharmaceutical company and maybe we have a financial interest and one of the great things about Yale and many other top institutions, is we have a lot of these trials that are really home grown science. They are based on discoveries from our

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own laboratories. They are then funded by the institution to test in patients, and we spend a lot of time discussing with patients, trying to walk them through that what we are trying to do further our knowledge of the disease and to develop new therapeutics and the good news that we always tell patients is that we have so many complex regulatory mechanisms in place to protect the patient and that is one thing that has always put patients at ease, that one of the first things, the top priority, is patient safety and making sure that we are not hurting anyone while still having a good chance of helping people.

Higgins That is a really important point because being involved in clinical trials myself, running a drug trial, it really opens your eyes to all of the things that happen before the trial ever gets to be enacted in the clinic. There is a whole institutional review board, human investigation committee and part of their task is safety, making sure the drug is administered safely, but also before the trial ever starts, thinking about what is in it for the patient and is it an ethical trial and I think that is important that as radiation oncologists, we end up doing a lot of educating, but especially when it comes to trials.

Bindra I totally agree.

Higgins Being an NCI designated cancer institute, we are fortunate to be able to offer these things to people, but one of the big responsibilities for physicians is doing the consent appropriately and getting the patient to understand what we are doing and why and especially in CNS tumors because it is scary, we are dealing with brain tumors.

Bindra We spend a lot of time on that in the clinic, trying to say that one of the advantages of a place like Yale is that we are going to offer what we think is best for the patient, and I spend a lot of time telling patients that I do not have a vested interest to have them do anything, but this is what I think will help you within a reasonable safety margin and we have many examples where we have pushed the envelope both on trial and what we call off protocol. It is something that in the last few years I have noticed with the talent pool of clinician investigators here at Yale that we are constantly pushing the envelope where we have what we call personal exemptions where we enroll a single patient for an off-label indication for a drug that is FDA approved for something else and it is those types of things that are really exciting to see happening at Yale.

Higgins And really exciting to offer because many patients they have run out of some of the standard therapy options, what we would think of as frontline treatment or even second line treatment and it is important for them to know when they are searching for additional therapies that these things are available at our institution.

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Bindra And that is one thing I always tell patients, when I was in medical school, I was a Yale medical student back in the early 2000s and I think you were my attending as you may recall, and I remember back then when people had brain tumors we had basically a plan A and if plan A worked there was really nothing else and what is really exciting now is we have a plan B, we have a plan C, we have a plan D and we can give you all those plans at Yale and it is very exciting to finally be able to offer patients other therapies that were not available before.

Higgins I am going back to the bench-to-bedside concept now which is before the trial comes to the clinic, there is a whole process of getting that drug examined usually in an animal model and that is again years before we ever get to the point where we bring it into the clinic, but maybe you could talk about some of the facilities we have and the ability to do these animal model studies.

Bindra I think one of the most exciting things about being involved in translational research right now is it used to be what you would call working in silos. We used to have what you called the Ivory Tower, Academics, very basic science setting and then you have the pharmaceutical companies in another corner of the room and seldom would you see them talk to each other and now what we are seeing happening is that academic institutions are now actually able to come up with ideas, run drug screens and then actually test the hits those screens in the animals within the academic institution and actually develop them towards phase I clinical trials. To that end, we have a drug screening facility here that is really second to none. Part of that is because in pharmaceutical industries, the landscape has changed. We have companies like Pfizer just down the street in Groton and as they downsize, we benefited from getting a lot of that talent and they now work at Yale and they have expertise in drug screening and it is so lucky for us because now we get to work with these folks who are top of the top for drug screening in an academic setting.

Higgins That has really become a great collaborative process, private sector academic, it is a win-win I think in a lot of ways and now we have the West Campus as we call it and that has been a huge resource. I do not think a lot of people know about that but that has been incorporated into our greater scheme of research and maybe you could talk a little bit about what happens over there.

Bindra The West Campus is almost another half of Yale now. Having been here in medical school and even as an undergrad in the mid-90s, things have changed here. When you walk over there, you realize that there is a sense of something exciting. We are able to sequence entire genomes for under \$1000. We can get the entire genomic profile of the tumor and we can present the results of that at Tumor Boards and we do. We actually have a Tumor Board on Mondays called Precision Medicine Tumor Board, and we just talk about the mutations that were sequenced over at West Campus, and what is really exciting is we have this entire side of Yale of translational science and a lot of it is brewing over at West Campus and it is really exciting to see it grow.

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Higgins And this concept that we have been trying to develop of personalized medicine, I think the era is here and we have these gigantic resources that are available to the patients to give them not just tumor specific but patient specific treatment, and it is really exciting to hear about the Precision Tumor Board. Could you talk about how exactly you are targeting things with that information you get from the people on West Campus.

Bindra I will give you an example, I do a lot of pediatric brain tumors and we have had patients that come, young kids with recurrent tumors, and know they have exhausted all other treatment options, and we have had some great examples where we can have our surgeon come in, maybe our neurosurgeon on staff will do a biopsy of that tumor, they will send it over to West Campus, and we have an infrastructure in place. This is by Dr. Gunel and Dr. Lifton, who pioneered these approaches in the genetics group here and they will actually sequence the entire genome of those tumor specimens. They will then be able to analyze that data and give us back information and the information we get is specific mutations and specific genes and at this Monday's meeting that we have, we are able to then say, well we have got XYZ, FDA approved drugs that target these, there is no indication to treat for this particular tumor, but can we find a way to make this work, and we have regulatory experts, we have phase I trial people that attend that weekly meeting like Pat LoRusso and Paul Eder and they will sit there and say, we can do this, we can make this happen and they will work really late that night and now get that personal exemption and get that single patient INDs, we call it, and get that drug for that patient which is really exciting.

Higgins It sounds like patients are coming from locations not just within New Haven or even within the county, people are coming from far away. How do they find out about these things? It is the referring physicians?

Bindra I think what has happened is we all know it is the information age and my phase I trial as I mentioned earlier where we are testing a drug from our lab, it is pretty remarkable, we get e-mails from people across the country that looked up our trial that someone in my presentations at a national meeting posted on line, I have a twitter account and it is always great to hear people read them, and I get calls, then they say well we heard about this trial.

Dr. Ranjit Bindra is Assistant Professor of Therapeutic Radiology and of Pathology. We invite you to share your questions and comments, you can send them to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC and as an additional resource, archived programs are available in both audio and written form at yalecancercenter.org. I am Bruce Barber hoping you will join us again next Sunday evening at 6:00 for another edition of Yale Cancer Center Answers here on WNPR, Connecticut's Public Media Source for news and ideas.