

Yale CANCER CENTER *answers*

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CNS Tumors and Gamma Knife

Guest Expert:

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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 on Myelodysplastic Syndromes. Yale Cancer Center Answers features weekly conversations about the research diagnosis and treatment of cancer and if you would like to join the conversation, you can submit questions and comments to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC. Tonight you will hear a conversation with Dr. Veronica Chiang about treating brain tumors with Gamma Knife technology. Dr. Chiang is Associate Professor of Neurosurgery and of Therapeutic Radiology at Yale School of Medicine. Here is Dr. Susan Higgins.

Higgins We are currently in the age of multidisciplinary therapy and our treatment of cancers is always now a team approach and I was wondering if you could tell our listeners how you as the neurosurgeon doing Gamma Knife therapy for brain tumors fit into this team.

Chiang There has been a lot of evolution in the multidisciplinary approach, probably over the past decade or so, and prior to this decade, neurosurgeons predominantly treated what we call primary brain tumors. These are tumors that arise from the brain itself. They can be benign or malignant and for most of these cancers the treatment is surgical. The more tumor that can be removed the better the outcome and for most of these tumors, a decade ago we knew that while radiation played some role in controlling the progression of these tumors, chemotherapy was typically not a great option for many of these diseases. What has changed over the past decade is the neurosurgeon's involvement in what we call metastatic cancer, this is cancer that has spread from outside the brain to somewhere else in the body such as lung cancer, breast cancer, melanoma, kidney cancer and more recently ovarian and uterine cancers and these cancers can spread to the brain just as they can spread elsewhere in the body. About a decade ago, neurosurgeons had very little to do with these cancers because by the time the cancer spread to the brain the outlook for the patient was not good and their survival was not expected to be long and so there was really no role for aggressive neurosurgical intervention. What changed this was the Gamma Knife and the Gamma Knife is a focused radiation tool that requires a neurosurgeon to aim the radiation to allow the radiation oncologist to deliver the radiation. The combination of having 2 specialists working together is really where the multidisciplinary concept for these tumors started to arise and so today, I participate not only in the surgical portion of removing tumors when it is appropriate but also delivering the Gamma Knife radiation treatment.

Higgins Just to step back for a second, part of the big picture with treatment of cancer overall is that within the body we are able to now control, with radiation, chemotherapy and surgery, the disease, what we call the extracranial disease, much better, so the importance of Gamma Knife in treating the disease in the brain has sort of come out of the advances we have made with treating disease in other parts of the body and now we know that the brain, even if you have cleaned up everything elsewhere, the brain is sort of a sanctuary site and that means that the chemotherapy agents cannot get there, which is where your expertise comes in, and we are finding that for a patient's

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quality of life especially, these tumors of the brain are often a big part of what happens in their disease process and we know that the symptoms are very difficult to control. Maybe we could just go on to talk about some of the technology. I always found Gamma Knife fascinating, I love the technology, I was on your team for a while and it was always so gratifying because it is actually a relatively patient friendly technology, I think because people are a little surprised at the end, it is overall a noninvasive technology, maybe you could talk about the process. What happens when a patient comes to you and needs Gamma Knife therapy?

- Chiang That is right, it is funny because Gamma Knife is a name that is a little bit scary and all patients have told me that over the years, but there is actually no knife involved and it is not a surgical procedure. As you said, the thing that is nice about Gamma Knife is that it is a single day procedure. It does require quite a few hours of investment in treatment but at the end of the day, we always promise that people get to go home and they are no different when they leave than when they walked in in the morning. The process starts with having something called a head frame put on. It is basically an XYZ coordinate box that has to be attached around the head so that we can localize in 3D space exactly where the tumors are in the head. This is the scariest part of the day. It requires instillation of some local anesthetic into the scalp and then the frame itself has to be attached firmly to the skull, but this takes about 5 or 10 minutes in the morning and really everybody usually does this very well. It is a little bit uncomfortable but it passes quickly and typically a little bit of sedation is administered in the morning to help patients through this part.
- Higgins Just to give some perspective on that, once the head frame is on, patients are basically sitting there, they can have fluids, they are sitting there drinking a cup of coffee through a straw, so once those few minutes pass, putting on the head frame, they are generally very comfortable right?
- Chiang Yes, these are similar head frames as when people break their necks and have to wear these devices around their head for months, so once the frame is placed, yes I think most of us say that it is actually more comfortable than the mask.
- Higgins That is right because it is open. I think when people hear about the frame they are not aware that these basically are a set of bars, but they can see, they can move around, it is just so that they can be immobilized in the actual Gamma Knife unit when we get to treating and that is the beauty of Gamma Knife that it can localize the tumor so well.
- Chiang Right, once the frame is put on, then the patient has an MRI in the frame and this allows us in 3D space to exactly localize where the tumors are. That information is then transferred into a planning system that has been well tested and well proven over many decades now and that allows us to pinpoint radiation exactly to where it needs to be delivered. As you said before, the patient is then put in the treatment machine and attached by the frame to the treatment machine so they cannot at all move their head in the machine and the machine knows where the tumors are in 3D space and

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all of the radiation can then be delivered all in one sitting very, very safely and incredibly, precisely and when that is done, then they come out of the machine, the frame gets removed, some small dressings are placed over the pin sites and most patients feel well enough to go home right away.

Higgins And part of the technology that I always found fascinating is that the imaging, which is a big part of this, the patients go for an MRI but these are not your average MRIs, these are MRIs with very high resolution and the treatment can really be directed to within a millimeter, correct?

Chiang Yes, the accuracy is in fact submillimeter. We make adjustments to the plan in the order of 10ths of millimeters and the other part of it, as you alluded to, is that the imaging is done on the day of the treatment, so if anything has changed between the time of consultation and the day of treatment, the Gamma Knife treatment accommodates for this and so what we see on the scans upstairs when we do them is what we treat to and if there are additional lesions seen also, they can be treated at the same sitting.

Higgins As we were saying, the patient comes in and it is a one day procedure actually. Morning till maybe the afternoon and then go home. Do they have after effects when they get home?

Chiang The only after effects that most people talk about are that they may have a very slight headache from having the frame attached and we do give some medicines obviously during the day, a little sedation at the beginning of the day that could still be floating around at the end of the day, so people do complain that they are a little bit tired, but we have a lot of patients who go back to work the day after this procedure, so we kind of equate it to going to the dentist.

Higgins I think it is actually more comfortable than any dental visits that at least I have been through.

Chiang Yeah that might be true.

Higgins What has always been fascinating to me is being able to sort of clean up the small metastatic lesions, some of which are really pinpoint small lesions and spare a lot of the normal brain can give people a big bang for their buck in the sense that we just talked about, quality of life and I think what many people are not aware of is that even small metastasis can cause a lot of neurologic problems that interfere with people's function. The other advantage here is that you are very effectively killing the tumor cells while sparing the normal brain tissue which we know is a really important part of what you are doing. Maybe you could talk a little bit about that because we as radiation oncologists have in the past treated brain metastases in many cases with whole brain radiation but the problem is that is a through and through process, all the tumors and the normal tissue get treated to the same dose. There is really a big difference when you are treating with Gamma Knife. Could you talk about that in terms of the advantages of Gamma Knife?

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Chiang Gamma Knife, particularly for brain metastasis, has evolved to address these issues. It used to be, probably less than a few years ago, that if you had up to 4 small lesions in your head, you could be treated with Gamma Knife, but if you had 5 or more, the recommendations were that you get whole brain radiation therapy, and as you and I both know, part of the problem with that is that if you have got 5 tiny little spots and a lot of normal brain, radiating all of that normal brain can ultimately, if the patient survives beyond a year or so, can result in cognitive side effects that are variable from person to person, but for some people, it can be quite debilitating, particularly if we can find these spots when they are small, the amount, or the volume, of tumor in normal brain that we are treating can be very small and therefore, the neurological consequences associated with that administration of radiation is inconsequential. I think we see Gamma Knife very much as a prophylactic tool and part of getting Gamma Knife is a phenomenon that we call surveillance, where patient should undergo MRIs or CT scans on a regular basis so that we can find these tumors when they are small, long before they are likely to cause symptoms and then we can deliver a minimum amount of radiation to get them under control. The Gamma Knife, in addition, allows us to deliver a lot more radiation at a single time and so even for larger tumors tends to be a lot more effective.

Higgins I would like to get to that in the second half but we are going to have to take a break for a medical minute. Please stay tuned to learn more about CNS tumors with Dr. Veronica Chiang.

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 and nearly 200,000 nationwide, but thanks to earlier detection, noninvasive treatments and novel therapies, there are more options for patients to fight breast cancer than even before. Women should schedule a baseline mammogram beginning at age 40 or earlier if they have risk factors associated with breast cancer. Clinical trials are currently underway at federally designated comprehensive cancer centers such as Yale Cancer Center and at Smilow Cancer Hospital at Yale, New Haven to make innovative new treatments available to patients. Digital breast tomosynthesis or 3D mammography is transforming breast screening by significantly reducing unnecessary procedures while picking up more cancers and eliminating some of the fear and anxiety many women experience. 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 talking today with my guest, Dr. Veronica Chiang about CNS tumors and treatment using Gamma Knife. During the first half we talked about the technical part of Gamma Knife and how effective it is. I think that one of the things that I as a clinician I have really been impressed with is that we are going through sort of a revolution in treating two particular types of cancers that spread to the

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brain, namely melanomas and lung cancers and using Gamma Knife with immunotherapies in ways that we have not in the past and we are seeing just tremendous progress with that and I was hoping that we could discuss that during the second half.

- Chiang This is really an exciting area actually, and this speaks a lot to the evolution of the multidisciplinary team that we have developed here at Yale for brain metastases specifically and that effort has been led by myself along with Dr. Harriet Kluger who is our melanoma specialist and Dr. Sarah Goldberg who has been our lung specialist who has worked with us as well as Dr. Scott Gettinger, so what we know about the effect of Gamma Knife on tumors is that while it does cause little tumors to disappear, bigger tumors, if they are found when they are larger, do not tend to disappear altogether and so there is, unfortunately, the possibility that down the line either we have not given enough radiation and the tumors re-grow or we have given too much radiation and we run into problems from the radiation itself, so one of the most exciting thing that started in melanoma and is now translating into lung cancer is that immunotherapies are becoming the latest treatment. Immunotherapies are drugs that rev up the immune system and teach the body how to go after tumors in the body wherever they are, and so what we believe now is that immunotherapies, while the drug itself may not necessarily get into the brain, the effector cells, or the T cells in the body, can actually get in just as they would do to clean up an infection, for example, they could also get into the brain and clean up cancer and so the most interesting developments that we have seen are in fact perhaps a cumulative or additive effect of giving immunotherapy along with Gamma Knife to get a better result with treating brain metastases.
- Higgins As we have discussed before, this whole idea of the brain being a sanctuary site, has really been a long-term challenge for us and I think that what is great is that we are finally seeing this new way to approach something that has always been really one of our last frontiers in treating and controlling the brain metastases from lung cancers and melanomas and the like, what we refer to in radiation therapy as radioresistant types of tumors.
- Chiang Right, and it is interesting because part of the advantage of Gamma Knife with whole brain radiation therapy initially was that because we were able to boost that dose of radiation delivered to the tumor with Gamma Knife, we thought that we had better control of radioresistant tumors compared with whole brain radiation therapy, but this boosted it to a whole new level.
- Higgins When we talk about the team approach, one of the things that I think people in general are not aware of is that we now have conferences where our special teams meet and we now even have multidisciplinary tumor boards for brain metastasis, not just brain tumors or CNS tumors and I think that is fascinating because this is really where we are making a lot of inroads where we can take a group and maybe we can discuss what happens at your tumor board because again this is the basis of how we are able to integrate all these therapies, the discussion starts at the tumor board, could you tell us what happens at the CNS metastasis/Gamma Knife tumor board?
- Chiang That is exactly right Sue, and part of the problem is that what you do not want for your patient is treatment based on who they get to first. What we want is evidence based, practice based, on what_

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you can achieve with each tool and what the side effects are so that we can balance what might be the best first treatment followed by what might be the best second line treatment and so what happens at the Tumor Board is we have representation from medical oncology, neurosurgery, radiation oncology and then we have pathology and radiology and so all of the patient's information is reviewed when it comes time to make decisions about what the next step of care is and if there is a good standard practice or recommendations for the next step, then those are discussed and recommended, but if there are no standard recommendations, in other words we are all scratching our heads a little bit about what to do next, it is also the place where options for discussion for clinical trials actually occurs and so out of our tumor board has come the pembrolizumab trial as first line treatment for untreated brain metastasis, led by Dr. Kluger. What we have done is we have offered patients pembrolizumab as treatment and if they respond to drug only, then this is the first time we have ever seen a drug that works both in the body and the brain and if it does not work, then we have obviously been able to treat those patients very effectively with Gamma Knife because we know that tool works for melanoma very well, so that is an example of how our patterns of practice have changed a little bit. It may not mean that pembrolizumab works for everybody but for those people for whom it works, then they have not had to come for Gamma Knife until perhaps later in their course and so that means there are potentially less complications and it is great that everybody is on the same page.

Higgins I do not think people realize that you may have 5 or 6 physicians with 100 years of clinical practice, cumulative clinical practice under their belt, as well as in many cases some of the people who work with us, the APRNs, the PAs, diagnostic imaging people are there, we are all talking about clinical trials and looking out for our patients and making sure that everything that could possibly help them, every tool that we have in our toolbox is going to be used, and as you noted, using it in the appropriate sequence and laying out a game plan upfront. I know that when we treat gynecologic cancers, we have the saying, we do not want to burn a bridge, we want to think upfront about how we are going to use all our tools and make them sequentially work in the best way possible for the best outcomes and I think that is the real blessing of being at an academic medical center for us and for the patients, practicing evidence based medicine and offering them clinical trials, we are trying to all work together as a team to get the best possible outcomes and this is really fascinating that sometimes you are saying now that treating with drug alone, immunotherapy alone and then doing the surveillance, is that correct?

Chiang Right, and as you alluded to, this comes from the fact that these are the first drugs that we think cross the blood-brain barrier into the brain but if you look at examples in the body, there are certainly times when we would start with chemotherapy and then boost that with radiation down the line and so we are looking at the possibility of this as we are getting back to your first point which is that people are getting longer and longer life spans following the initial diagnosis of their cancer.

Higgins Right, we have a long term view of the patient and we are thinking maybe upfront we are going to use the drug first and then we are going to, as I say to patients, we have other tools in our toolbox but we keep them in our back pocket until we need them because again we are also trying to find

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this balance between basically getting control of the tumor cells but not damaging too much in the way of normal brain cells or normal tissue. So it is a really fine balancing act and again I think that the upfront discussion that we have at the tumor board gives us probably the best chance of getting that long term outcome that is a good balance between those two things.

Chiang It does and like you said, it means that everybody on the team knows what we are doing at any particular time so it lessens the chance of a miscommunication and that is particularly important when looking at the pathology and the radiology because in some ways, they never get to see our patients and so their interpretation of information is also very dependent upon clinical input, so having everybody in the same room together means that there is just no misinterpretation.

Higgins Because although we have the EMR and everybody can share the information there, there is nothing really that replaces the face-to-face with the diagnostic radiologist who plays such a big role, I mean I have been in tumor boards, we are giving them information that basically, they will say, oh! Okay now that we know that, we are thinking a little differently about what we see on the skin and one of those things that comes up all the time is when we look at the tumor after treatment, we are looking at has it responded and is it dying or is this a side effect called necrosis and that is always a big dilemma for us, how to approach that, and I know that there are some new things that are coming out to help us with that, can you just give us a brief overview of that topic?

Chiang Actually it is a pretty big topic but I will try and make it fast, so what we have learned over the years is that radiation, like a sunburn, carries its own set of problems if you live long enough, the biggest problem, however, has been exactly what you said, which is differentiating regrowing tumor from the side effect otherwise known as radiation necrosis and prior to this there were no great options for either treating a re-growing tumor or radiation necrosis but more recently, there have been some new drugs, something called Avastin and new procedures, something called laser and coagulation that have been highly successful at treating radiation necrosis and now for the first time, it is actually really important for us to try and work out which of these it is because if you have radiation necrosis there are actually some really good options available now for treating this and so we are less worried about the side effects of radiation and really more concentrating on our first bang for the buck treatment for tumor and this is kind of where the multidisciplinary group comes in.

Higgins Yes, I remember the days where that was really the wall that you hit, we had the ability to retreat and we had the ability to use radiation in the scenario of using Gamma Knife over and over but eventually we had a tumor that was either too big or had been treated too many times, we had necrosis and that is where sort of the story stopped, so this is a new frontier, getting past the tumor regrowth and/or necrosis which used to be just a stopping point. We were then out of options.

Chiang That is exactly right and we are going to run into this more and more as people live longer and longer, but the ability to delay the use of some of these tools also allows us not to run into these complications as early.

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