

00:00.000 --> 00:13.700 Support for Yale Cancer Center Answers comes from AstraZeneca, providing important treatment options for various types and stages of cancer. More information at astrazeneca-us.com. 00:13.700 --> 00:39.500 Welcome to Yale Cancer Answers with doctors Anees Chagpar and Steven Gore. 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 brain metastasis and gamma knife with Dr. Veronica Chiang. Dr. Chiang is a Professor of Neurosurgery and Dr. Chagpar is Professor of Surgery at the Yale School of Medicine. 00:39.500 --> 00:44.800

Chagpar So, Veronica, maybe we can start off by talking about what exactly are brain metastases?

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Chiang So, brain metastases are cancer in the brain that has spread from some place else in the body. And so, there are lots of different cancer types in the body -- lung cancers, breast cancers, thyroid cancers, GI cancers, and unfortunately what we have discovered is that the longer that you live, the more likely it is that any of these cancer types can in fact spread through the blood stream and end up lodged in the brain. And in the brain, there is not a lot of escape mechanisms from there, and so, because of that the cell lodge and then sometimes they can grow and if they start to grow, then they start to cause trouble and so these are known as brain metastases.

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Chagpar So, a lot of people when we think about metastatic disease or metastases that have spread outside of where ever they started, they went to the brain, the lung, the liver, wherever - that often is not something that we can treat for curative intent. So, usually and not always, but usually, these are things where surgery is really not indicated?

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Chiang So, I think that that is true probably for a larger percentage of patients, but I think it depends on how the cancer has spread. So, if we take lung cancer for example, not all lung cancers are the same. So, there are some lung cancers that have what we call oligo-metastatic spread, where there is just one spot in the lung and then perhaps one or two spots in the brain. And if that is the case, then if it has not spread to any place else, then in fact it may be curable. Obviously, the other end of the spectrum is somebody who has got spread to brain, bone, liver, adrenals and everywhere, and for those patients, I think the ability to cure those people is more dependent on the ability to control the disease throughout the body and that is usually with medical therapy.

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Chagpar Right. And so, for a particular subset of patients where the disease

is really limited to one or two sites, potentially even if the disease has spread outside of its original organ, we can do something about where it has spread to, which is where I guess your whole area in terms of gamma knife and neurosurgery comes in with these brain metastases. So, tell us more about who is eligible for that.

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Chiang So, when I first started in practice about 20 years ago, there were very few patients who were eligible. I think part of the issue was that by the time patients were found to have these metastases in the brain, they had a large number usually of lesions and the only treatment that was available back in that day was something called whole brain radiation therapy, which is still existing today and is still very good treatment but has some neurocognitive side effects that we like less today. So, two things have happened over the years. The first is that gamma knife is not a surgical procedure - it is actually a radiation procedure. So, it is a 1-day focused radiation treatment, and so, radiation just like whole brain radiation therapy has been around for a long time. Gamma knife is just - it is a specific machine that was created to allow us to focus radiation just to the areas of the tumor, trying to spare the radiation to the normal brain cells. And what has been great about this technology, it did start off back in the day where we only treated a few lesions at a time, but there are many centers around the country now that can treat in the order of 20 or 30 lesions at a sitting. And so, it is really just, so from a radiation standpoint, it is just more appropriate for a larger number of patients because you can treat a larger number of lesions at each sitting.

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Chagpar And so, when we think about radiation, you were saying that gamma knife is just a 1-day treatment?

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Chiang So, it is right. And so, the concept behind it is, is that with standard radiation, standard radiation was originally prescribed to large fields, so large areas of the body, and so, the more normal tissue that you radiate, the more toxicity there is. If you can limit the amount of normal tissue that is being radiated and just aim at more at the tumor, then there tends to be a far less toxicity. And so, radiation, the way it works is that the higher the dose of radiation you could administer all at one time, the more effective it is against tumor. Obviously, the reason for having it divided into small doses over long periods of time is to protect the normal cells. So, with the gamma knife if you can aim most of the radiation at the tumor, then you want to try and give it all at one time and that is why it is a 1-day treatment.

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Chagpar I think patients most love it?

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Chiang Well, patients do love it except for at the beginning of the day where they have to have a targeting device attached to their head, and that thing is attached by 4 screws to the bone which nobody particularly enjoys, but what it does allow us to do is, is to do the mathematical planning and the physics planning that is required to allow that treatment all in that 1 day. So, from an efficiency standpoint and certainly from a delay in getting to next steps of therapy standpoint, it is a very popular tool. And so, actually, as gamma knife was growing about a decade ago, I think the real adopters were the medical oncologists because this was a way to get the brain disease treated without any interruption in their chemotherapy.

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Chagpar And I can imagine that they would have really loved it because some chemotherapy does not get past this blood-brain barrier and get to the brain, and so, being able to focus an ablative therapy at a cancer in the brain without having to worry about the blood-brain barrier must have been very appealing?

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Chiang Yes, yes. I think that is exactly right. So, chemotherapy could not have been dependent upon back in the day to cross the blood-brain barrier, and so, yes treatment of brain metastases was kind of one of those things that took priority over everything else.

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Chagpar And the other thing that seems to be is really nice about this whole gamma knife concept is the fact that -- A. It is not invasive, so it is like somebody is opening your skull and trying to take out this cancer surgically, but rather is doing this through your brain with radiation. And the second is, that versus surgery which presumably is another way to remove brain metastasis, this really is easier in terms of being tolerable?

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Chiang Yes. Well, so some of my patients who have had surgery, prefer surgery because they go to sleep for their sleep. But you are right. I think from a recovery standpoint, many of our patients will go back to their normal activity the following day. And so, you are right from the recovery standpoint, this is much more tolerable.

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Chagpar So, tell me, are we using gamma knife for curative intent, that is to say, somebody has a brain metastasis, we can see it on a CT scan, it is not particularly bothering them but it is so limited in terms of its disease that we can eradicate it and make these patients what we call "NED," no evidence of disease, if we can remove the lung cancer and get rid of the brain metastasis, that

is done. So, are we using gamma knife in that cohort of people and/or are we using it for people who have a brain metastasis where it is actually impinging upon structures that are causing problems, they are getting the seizures or something that is because this tumor that is growing in their brain is actually pushing on something that is not meant to be pushed on, and we are using gamma knife to ablate it such that they are no longer having those seizures or whatever other issues they might be having?

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Chiang So, we are using it for both. So, I think the use of gamma knife is divided into probably three main cohorts. So, the first one is actually purely prophylactic treatment. So, not necessarily for curative intent where there is ongoing metastatic disease in the body, staging MRI scans show new spots that are showing up in the brain that are appearing despite whatever medicine you are on for your cancer, and so, we are treating these spots to stop them from growing so that they do not cause you trouble in the future. So, that is the biggest cohort of patients that we are treating today. The second is, the symptomatic one, that you mentioned where these spots are growing somewhere and they are causing swelling in the brain, that is causing a neurological deficit or seizures or otherwise. They are a smaller percentage, but because we are hoping that people are getting those screening MRIs and these are being found earlier so that we do not get to this point, but certainly there are people early in their diagnosis who might not know that they had cancer or people who actually have been, like you said, NED in the body who then pop up a new spot in the brain, and so, for those people, gamma knife can be very effective for symptom control. And I think, the smallest group is the group that you talked about for curative intent. So, we do not necessarily believe, so I think most of us do not believe that radiation is necessarily curative. So, the way radiation works, what I tell my patients is that it breaks the DNA within the cells; if the DNA is broken, the cells cannot divide, but it does not guarantee that the cells will die off, and so, repair of that DNA can subsequently allow them to regrow. And I think that one of the challenges with gamma knife is that if you live long enough and you are in fact NED in the body, that gamma knife in and off itself may not be 100% curative. And so, what we do think is that if in fact you want to go for cure, that you might consider surgery as an option to remove the majority of the tumor before giving you consolidative radiation to the area and that gives you a better chance.

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Chagpar And so, when you say consolidative radiation, are you talking about whole brain radiation or gamma knife?

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Chiang Well, it can be or gamma knife right. So, depending on the size of the lesion obviously. So, usually with smaller lesions, resection and gamma knife. Obviously, if it is a large symptomatic lesion, however, but single, then control

of symptoms and control of disease is still better with surgical resection followed by possibly larger field radiation or whole brain.

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Chagpar And so, if people have gamma knife versus whole brain radiation, what is the difference in terms of, I mean, clearly there is a difference in terms of time course, what is the difference in terms of those neurocognitive deficits that people get? I mean, how does that work?

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Chiang So, with whole brain radiation therapy, there is a risk for neurocognitive decline. It does not happen to everybody. What is difficult to know is who is going to get it, and what happens is that, it starts to occur around a year or so and gets worse the longer that you live. Whereas, with gamma knife, obviously the more focused you can be with radiation hopefully, the less cognitive decline you will have.

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Chagpar Excellent. Well, you know, we want to take a very quick break for a medical minute. But hopefully, we will come back and learn more about brain metastases and gamma knife with my guest, Dr. Veronica Chiang.

14:02.000 --> 14:20.900 Medical Minute Support for Yale Cancer Answers comes from AstraZeneca, a global science-led biopharmaceutical business committed to bringing to market innovative oncology medicines that address unmet needs for people living with cancer. More at astrazeneca-us.com. 14:20.900 --> 15:01.900 This is a medical minute about head and neck cancer. Although the percentage of oral and head and neck cancer patients in the United States is only about 5% of all diagnosed cancers, there are challenging side effects associated with these types of cancer and their treatment. Clinical trials are currently underway to test innovative new treatments for head and neck cancers and in many cases, less radical surgeries are able to preserve nerves, arteries and muscles in the neck enabling patients to move, speak, breathe and eat normally after surgery. More information is available at YaleCancerCenter.org. You are listening to Connecticut Public Radio.

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Chagpar Welcome back to Yale Cancer Answers. This is Dr. Anees Chagpar, and I am joined tonight by my guest Dr. Veronica Chiang. We are talking about brain metastasis and gamma knife, and as all of you know and as we talked about before the break, brain metastases are really cancer spots that have broken off from where the cancer started and landed in the brain. And Veronica, you were telling us about gamma knife as kind of a high-intensity, very focused radiation that can sometimes get rid of albeit of maybe not a 100%, but really reduce these brain metastases and one of the questions I had was what about people who present with a primary brain cancer; like, not spread from

somewhere else but a primary brain cancer, is gamma knife a treatment that they also can avail themselves?

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Chiang So, gamma knife for primary brain tumors, mostly we are talking about high-grade, you know, like glioblastoma, I think that that topic remains somewhat controversial. Gamma knife because the dose is delivered all in 1 day is limited by its volume of radiation that the area of the brain that can be treated. And so, we talk about 3 cm as being the largest diameter that we can safely administer radiation to. The problem with primary brain tumors is that when we look at the scan, where we think the cancer is, is not limited to the area that takes up the dye, so when we do MRIs, we administer something called gadolinium and then that looks white, that is the area that looks white on the scan; and so, in addition to that, when we do the MRIs, we look at abnormal water content within the brain and there is always an area surrounding the white contrast-enhancing area that lights up as well. And so, to really use the gamma knife to target all of the primary brain tumor, one would have to target the entire area that has got abnormal water, not just the area that lights up with dye and that is very rarely less than 3 cm in diameter.

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Chagpar Could you use gamma knife in a primary tumor after surgical resection, kind of like we were talking about with the brain metastasis where you might take that out and use either gamma knife or whole brain radiation?

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Chiang So, typically the standard of care is actually to give fractionated. There are very few situations in which a small tumor is identified resectable and then you can give gamma knife to. And so, because of that, I think you know standard fractionation is 54 to 60 Grade, you know, divided into small doses....

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Chagpar Treating the whole brain?

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Chiang No treating the field. Yes, so treating that whole area that lights up, the abnormal water...

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Chagpar But that is still more than 1 day because you have to divide it into these fractions?

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Chiang That is correct, that's correct.

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Chagpar And you have to divide it into these fractions because you are covering a bigger area and because you do not the rest of your brain to get toxic from having a very high dose all at one time?

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Chiang That's correct, that's right. And so, there is probably more literature talking about using gamma knife for recurrence of disease. So, sometime when, so now we are watching regularly to see if things are stable, and when disease recurs, it often recurs in a small nodule, and so there is an increasing amount of literature that suggests that perhaps those small nodules might be treatable with gamma knife. The problem with those situations though is that we often run into toxicity from too much radiation in the brain, something called radiation necrosis. And so, these are, you know, the debate about what the right tool is for treating recurrences is still ongoing.

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Chagpar Well, it sounds like, you know, things have really changed over the last several decades, you talked about when you started your career - how things were very different, and now with gamma knife, at least for brain metastases, we have a new technology that can focus radiation in these areas and potentially help either preventing them from causing problems or dealing with symptomatic lesions or potentially in a very small number of cases actually helping people achieve what could potentially be a curative lesion if they do not have other disease. Tell us about some of the other advances that have happened in terms of treating brain metastases or are we done, gamma knife is it - there is no more advancement?

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Chiang So, I wish gamma knife were it, but...

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Chagpar No kind of nice that the field keep moving because I think that once we hit, if we ever get to the point where we say, you know what, this is it, this is the best that we get, it would better be perfect.

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Chiang So, there have been 2 major advances in the treatment of brain metastases. So, the first is on the technology side where gamma knife is no longer the only radiosurgery capable machine that is out there, and so there are very many other machines that do not necessarily require a head frame where radiosurgery can be administered by a mask, and so this is often easier. So, patients who have like 1-5 brain metastases can be treated using a mask-based machine. Unfortunately, the complexity of the physics planning means that if you have got more than that you still have to come and have that thing screwed on your head. But, so that has been a significant advance from a patient comfort standpoint. In addition to that, on the medical oncology side, there has been significant

advancement in the medicines that are available and so remember we talked about the fact that chemotherapy did not cross the blood-brain barrier, but there are new medicines called immunotherapies and targeted therapies that in fact, so targeted therapies we think actually cross the blood-brain barrier very well, these are very small weighted molecules and it is not completely clear why they are able to cross the blood-brain barrier, but the drug companies seem to have found that magic component, and so, many of these drugs can cross quite effectively, especially if the brain metastases are found when they are small. And so, this has changed our paradigm about how we think about what might be first-line treatment for brain metastases, and sometimes it is drug and not necessarily radiation.

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Chagpar And so, would it ever be drug alone or is it always combined with radiation as well?

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Chiang So, there is certainly a big push on the patient and medical oncology side for it to be drug alone. There is no randomized study yet looking to see which one is better. There is a lot of retrospective data, however, that suggests that combination is still better for long-term control than drug only, but certainly starting with drug and then considering radiation as part of the treatment is perfectly reasonable today.

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Chagpar And getting back to the technology bit, I mean, I think that everyone who is listening must have been shuddering as I was when you talked about having 4 bolts screwed into your head on the morning of gamma knife radiation, and that really is just to fixate the head in one position so that the beams of the radiation are where you intended them to be?

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Chiang Yes. So, you know, radiosurgery treatments because they are 1-day treatments tend to be long right, so with whole brain radiation therapy, you come in each day, you have a mask put on and you stay in that mask for 5 or 10 minutes at most and then you go home and you come back and do the same thing the next day. For us to administer all of that radiation all at one time, however, the treatments are 30, 45, hour and a half, two hours long and for you to lay perfectly, perfectly still for that amount of time is almost impossible. And so, people need to be sedated even if they are in their mask and they need to be cooperative so that they can actually stay still because there are small degrees of movements that are still possible within the mask. And so, with the head frame, you are completely locked in place and it takes that onus away from the patient and allows them to sleep or whatever they do while the treatment is being delivered.

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Chagpar But there must be a better way to make sure your head is staying in a spot, like put bolts or walls attached to a bed that your head goes in that it cannot jiggle around, but put the bolt in the bed and not in my head?

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Chiang The issue is the relationship of your head to the bed and so, you know, patients will tell you that actually for long, long treatments it is actually much easier to have the screws put in. It really allows, the head frame is open and once you are immobilized, you do not really notice as much. The mask actually covers your entire face and so, if the patients who are claustrophobic, that can actually be a really big problem.

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Chagpar And so, these bolts are put in while you are awake, do you use like local anesthetic, do you feel these things like?

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Chiang Yes. So, the worst part of the day is actually putting in the local anesthetic. It is like getting the Novocaine from the dentist or you know getting your local anesthetic before they access your port or whatever. So, the medicine - it burns as it goes in and there are 4 spots on the head, but actually once it goes numb, then having the screws put in is, many patients have described it as some anti-climatic.

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Chagpar Okay. I still think that you guys can do better on that one, but tell me about other things. You know, when we think about ablation, and certainly this is something that a lot of different cancer types have thought about, in terms of either focused radiation or lasers or freezing things or microwaving things, I mean have we thought about other ways of getting rid of brain metastases that may be better or different or in some way more reliable than gamma knife?

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Chiang Yeah. So, I think that technology is coming. So, there is a new surgical tool called laser thermocoagulation that was actually developed initially for deeper targets for things like movement disorders, but the concept is kind of the same, you know, you put a laser into the head and then you know you burn out your target from the inside. The biggest challenge in the brain was knowing how long to burn for. So, back in the day, we used to stick the radiofrequency ablation devices in and we would turn them on for 3 minutes at 80 degrees and what we found when we imaged these patients after surgery was that there was a highly variable size of lesion that was created after the surgery. And so, the reason for its resurgence today though is something MR thermometry; and so, using the MRI, we can look and estimate temperature changes within the brain.

And so, by taking those images and putting them into a complex computer, you can then start to predict for how long each voxel has been delivered how much heat. And you can take those 2 parameters and calculate through something called Arrhenius equation where you might have actually killed off cells. And so, software that is available now allows you in a color picture to see where you actually think you have heated, to what extent and you know, does that heat in fact cover the lesion that you think you wanted to heat. So, we then took that from the functional surgeons and started to use it for tumors. And so, what has been really nice is, so we have not really used it yet for people with first-time tumors because obviously gamma knife is a very reliable treatment tool right now, but after you have had gamma knife one time, if the lesion regrows in the same area, then we are a little bit limited by what options we have available to treat you because the second round of gamma knife can cause all kinds of radiation problems. And so, we have been able to salvage people with these problems by putting the laser into the middle of these tumors and burning them from the inside. And so, we have a growing experience with this, but it is a very exciting and novel tool that is coming up.

29:00.900 --> Dr. Veronica Chiang is a Professor of Neurosurgery at the Yale School of Medicine and Director of the Gamma Knife Center at Yale Health. 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. We hope you will join us next week to learn more about the fight against cancer here on Connecticut Public Radio.