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CENTER

answers

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Gamma Knife for Cancer Treatment

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Welcome to Yale Cancer Center Answers with doctors Francine Foss and Lynn Wilson. I am Bruce Barber. Dr. Foss is a Professor of Medical Oncology and Dermatology, specializing in the treatment of lymphomas. Dr. Wilson is a Professor of Therapeutic Radiology and an expert in the use of radiation to treat lung cancers and cutaneous lymphomas. 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 evening, Francine and Lynn welcome doctors Jonathan Knisely and Veronica Chiang. Dr. Knisely is an Associate Professor of Therapeutic Radiology and Co-Director of the Yale-New Haven Gamma Knife Center, and Dr. Chiang is an Associate Professor of Neurosurgery and of Therapeutic Radiology, Director of Stereotactic Radiosurgery, and Medical Director of the Yale-New Haven Hospital Gamma Knife Center. Here is Francine Foss.

Foss I would like to start off by having you tell our listeners a little bit about your backgrounds and how you became involved in your respective fields.

Knisely I will go first. My realization that radiation oncology was the field I wanted to go into, was predicated upon the realization that there would be CAT scans and MRI scans available ubiquitously. It was not something where people had to debate, gee; do you think we should get a scan? And that was concurrent with the availability of digital desktop computers, which would be able to figure out exactly where things were in three-dimensional space and be able to aim the radiation where the problem was and avoid the stuff that did not need to be treated. The transition from that to radiosurgery was very, very simple because neurosurgery was a field in which everything got pinned down with a stereotactic frame for a biopsy or a procedure and there was no issue with movement, and the availability of MR Imaging allowed us to see exactly where things were in the brain with a much higher degree of accuracy than elsewhere in the body.

Chiang From my perspective, I was a young neurosurgeon, looking for a career, and radiosurgery was a developing field particularly in the area of metastatic tumors. I think that, certainly, over the last 10 years, this field has moved from something that was considered relatively novel to something that has now become pretty much standard of care, and what was required was emerging between the medical oncology field, the radiation oncology field, and the neurosurgeon to allow comprehensive management of these lesions, and so this was good for me.

Wilson Jonathan, can you tell us exactly what gamma knife is? We hear the word “knife” and I think some people assume that there is a surgical aspect to this. Tell us the details about this and when it was first developed.

Knisely The gamma knife’s original concept dates back to the early 1950s. Brain surgeons trying to do operations back then had the same challenges that we have currently with identifying exactly where the target is, the thing you are going after. A neurosurgeon named Lars Leksell in 1949 developed a stereotactic frame system to allow biopsies to be done. About two years after that, he realized that the trauma associated with conventional neurosurgery in going in and getting the thing out might be able to be avoided by using convergent beams of radiation that were highly focused, directed at the site of what was going to be removed, directed at the tumor, and that led to

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a number of prototypes that they tried in Sweden. The first working model of the gamma knife was in 1968 in Stockholm, and again, it took some time, really until you had good high-speed computers and good three-dimensional imaging that would allow you to see exactly where the thing you wanted to hit was, to be able to target the radiation as accurately as we can currently. The gamma knife uses about 200 very highly focused radiation beams that come from all different directions, not just in one plane but in many planes simultaneously to aim radiation at what you are trying to destroy or stop the growth of and by having, for example, 200 radiation beams coming altogether, each of the individual beams is only delivering 1/200th of the dose of radiation that the tumor gets so that the dose to the normal brain cells is much, much lower, and more likely to be very well tolerated.

Foss Can you tell us, Veronica, about stereotactic surgery and also about the impact of the gamma knife on what you do as a surgeon?

Chiang I think that for neurosurgeons, stereotactic surgery has been around for a long time. Typically we will put patients to sleep and this is a technique that has been practiced on animals previous to this to make sure that the technique was safe. We have used it a long time, as Dr. Knisely suggested, targeting things that are deep in the brain. It started particularly with the treatment of pain and movement disorders, and in fact, when Lars Leksell started, that was really the goal of offering radiation to that area. This has then translated in the operating room now to modern day where we use it to guide where a craniotomy is made to make the smallest incision possible, but it also allows us to resect lesions more completely, and obviously, there are still places that we cannot go and so what we cannot achieve from a surgical perspective we can now achieve with the radiosurgical treatment. We can aim radiation at places where we cannot go surgically or we do not want to go because patients are inappropriate for surgery.

Wilson Jonathan, what are some of the primary indications for gamma knife? What types of patients do you see and manage with this technique, which has obviously evolved tremendously over the last 40 years?

Knisely We are seeing approximately 60% of our cases having metastatic disease to the brain. The common tumors that spread to the brain include lung cancer, breast cancer, and melanoma. We also see many patients with other types of tumors. Tumors that spread to the brain are very commonly referred for treatment on the gamma knife. We see a number of other tumors that start in the brain; tumors such as meningiomas, pituitary adenomas. We treat vascular malformations, arteriovenous malformations, and vascular tumors. We treat conditions such as trigeminal neuralgia, which is a very painful condition affecting the face. We have treated skull based tumors, tumors arising in the paranasal sinuses that have spread to the orbits. As Veronica indicated, this technique was originally developed for movement disorders and pain syndromes so we have done that in the past but we do not have a current active program with movement disorders. We have actually even treated somebody with epilepsy.

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- Foss Can I ask both of you how you determine that a patient is eligible for gamma knife? Do you have a combined modality clinic or do the referrals come in and one of you sees them?
- Chiang What has made it most efficient for us, and this has really just evolved over time, is that the consultations predominantly come through one coordinating center and for now that is most effectively coordinated through the neurosurgical services, the main reason for that being that the neurosurgeons have been subdivided somewhat into their sub-specialties. So, if you had metastatic disease, you would be referred to my office. If you had a vascular malformation, you would come through Dr. Gunel's office, etc., and it is that office's responsibility to make sure that there is a consultation both with the neurosurgeon and with the radiation oncologist. We have made a concerted effort for those consultations to be either performed at the same time or at least on the same day, so it makes for a single day visit, and then what we have been able to achieve, certainly with metastatic disease because of the urgency with which these patients need to be treated, is for their treatment to most often occur within the same week.
- Knisely Francine, the way I explain it, or I think of it is like a Venn diagram where surgeons can either use conventional microsurgical techniques or radiosurgery, and I as a radiation oncologist can use fractionated radiation therapy or radiosurgery. We have to concur that radiosurgery is a good option for that patient and make sure the patient understands the risks and benefits of the different approaches that might be applicable, and it is common for us to also recommend observation for patients because many of the tumors that we might treat with the gamma knife are benign and we want to make sure that the patient actually has a tumor that is causing some loss of function before we recommend an intervention.
- Foss Would there be a situation where you may do surgery and use the gamma knife?
- Chiang Yes, certainly. I think that there are some situations where the tumor may either be too large for its location or just too large overall, or where there are multiple lesions, and so some of them may need to be addressed surgically and then the rest of them could be addressed with radiosurgery.
- Knisely We also use radiosurgery with radiation therapy. It depends on the clinical situation.
- Wilson Jonathan, can you talk us through the actual procedure? Obviously our listeners may think of traditional surgery, neurosurgery, it is a hospital stay, general anesthesia, very long procedure that may take most of the day for Veronica and her colleagues? What is involved in the gamma knife procedure itself?
- Knisely Once the decision has been made to offer radiosurgery and the patient understands the procedure is scheduled and that usually means the patient comes to the hospital early in the morning, and once they have been confirmed to have a heart that is beating and they have got an IV started, then local anesthetic is administered by Dr. Chiang to four spots on the scalp so that a stereotactic frame can be put on the patient's head. This is basically a temporary guidance system, literally a frame of

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reference that will be used for determining exactly where the radiation should be aimed. Once that frame has been put on, the MRI scan and/or CAT scan that is used to obtain the three-dimensional coordinate system for the procedure is done. That takes about 20 minutes. The patient will come back to the Gamma Knife Center and we will then review the imaging, come up with a plan and that can take sometimes 20 minutes, sometimes an hour or more. Once that plan has been generated, reviewed by Dr. Chiang and myself together with a PhD physicist, we take the plan that has been created in virtual reality and transfer it to the computer system that will control the treatment, we bring the patient in, hook the patient up to the machine that will control the positioning of their head so the radiation is aimed with submillimeter precision, and the treatment is then delivered. Very simple treatments might only take a half hour of time in the machine. More complex treatments where many different spots might need to be treated, might take several hours, but generally it is an outpatient procedure. At the end of the procedure, the head frame is removed, bandages are put on where the head frame had been attached, and we discharge the patient from the hospital.

Foss Is this done in a special Gamma Knife Center or is it done within your department?

Chiang We actually have a small area that has been designated for gamma knife patients and the procedure. We are, however, part of the radiation oncology department and so we are one of the, I think, six or so vaults down there.

Knisely In the basement of Smilow Cancer Hospital.

Chiang Yeah.

Foss We have talked a lot about brain tumors and I am wondering, do you use this technique for other kinds of spinal cord tumors or other areas that might be difficult to get to?

Knisely The gamma knife was developed by a brain surgeon for use in the brain and there are some limitations in its design that preclude it from being used for tumors too far below the bottom of the skull. We have other technological platforms that we can use to address tumors that occur lower down in the neck or down in the spine.

Wilson Is gamma knife available, Jonathan, in other centers around the United States or in Connecticut?

Knisely There are no other gamma knives in Connecticut. There is a gamma knife in Providence. There are a couple in New York City and its immediate environs. There is one in Boston. It is a technology that has been recognized as being very valuable and many other platforms have been developed to try and duplicate what the gamma knife can do using other approaches to focus radiation very precisely on very small volumes of tissue.

Wilson Let's address that when we get back from our break. We are going to take a short break for a

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medical minute. Please stay tuned to learn more information about gamma knife with doctors Knisely and Chiang.

*Medical
Minute*

The American Cancer Society estimates that in 2009 there were over 65,000 new cases of melanoma in this country. Over 1,000 patients are diagnosed annually in Connecticut alone. While melanoma accounts for only about 4% of skin cancer cases, it causes the most skin cancer deaths. Early detection is the key. When detected early, melanoma is easily treated and highly curable. Clinical trials are currently under way at Yale Cancer Center, Connecticut's federally designated comprehensive cancer center, to test innovative new treatments for melanoma. The Specialized Programs of Research Excellence and Skin Cancer Grant at Yale, also known as the SPORE grant, will help establish national guidelines on modifying behavior and on prevention as well as identification of new drug targets. This has been a medical minute brought to you as a public service by Yale Cancer Center. More information is available at YaleCancerCenter.org. You are listening to the WNPR Health Forum on the Connecticut Public Radio Network.

Wilson Welcome back to Yale Cancer Center Answers. This is Dr. Lynn Wilson and I am joined by my co-host, Dr. Francine Foss. Today, we are joined by doctors Jonathan Knisely and Veronica Chiang and we are discussing gamma knife. Veronica, could you talk to the listeners a little bit about both short- and long-term side effects, if there are any, related to the gamma knife and review some of the expected benefits of the treatment?

Chiang One of the reasons why gamma knife has become so popular as a tool is that there really are not too many side effects from the gamma knife treatment itself. The advantage of the gamma knife is that compared to other radiation tools that have been used in the past, the amount of normal brain that receives radiation is relatively small compared to tools such as external beam radiation or even IMRT, and certainly compared to surgery, many of the approaches that we use surgically require entry through normal brain to get to deeper tissues and tumors and so there is very little of that involved. As Dr. Knisely had discussed before, there is obviously no knife cutting and no opening of the skull and things like that and so these are all clearly benefits of undergoing gamma knife. Gamma knife, in addition, is a one-day procedure, so there is no admission to the hospital, there is no general anesthesia, and all of these things, particularly for patients with metastatic disease who have a lot of other disease going on in the rest of their bodies it is clearly an advantage. The side effects of radiosurgery mainly depend on the size and the location of the lesions themselves. In general, with lesions smaller than a centimeter in size, radiosurgery rarely causes a problem. As the lesions start to increase slightly, larger than that up to about 3 cm, which is the limit of gamma knife, there can be some swelling from the single dose of radiation, but this can usually be treated with a dose of something called Decadron, which is a medical steroid that we use and those effects are transient. Unfortunately, radiosurgery can sometimes bring on seizures. What we have done in our center is we have treated people with a pretreatment dose of anti-seizure medicine and that in general has averted seizures from occurring. Down the line, what we have been seeing is that

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some people unfortunately, as with other forms of radiation that have been delivered, the tumors can start to re-grow again, but obviously, this is possible with any tool that we use, and I think that the rate of re-growth with radiosurgery has been inordinately low compared to some of the other tools out there that we have available to us.

Foss Veronica, is there a limit to the number of lesions that can be radiated at any one given time?

Chiang Actually there used to be. It depends on the machine that you have. We, very fortunately, have been able to upgrade recently to the latest version of the gamma knife known as the Perfexion and this machine was specifically designed to treat multiple metastatic disease, and so while we used to have a limit of around 10 or 15 lesions because it just took a long time to treat those people, we actually have been able to treat up into the 30 to 40 lesion range per sitting with this machine.

Foss Jonathan, I had another question about side effects. If you compare your patients who have had whole brain radiation to those who have gamma knife, the whole brain patients oftentimes complain of fatigue and then they have these kind of memory changes that are transient, do you see that with gamma knife?

Knisely It is much less frequent with gamma knife. The dose to normal brain structures is much lower. There actually was a randomized control trial, a scientific study that looked at radiosurgery alone versus radiosurgery plus whole brain radiation therapy for patients with between one and three brain metastases. This was a study conducted at MD Anderson Cancer Center in Houston. They found that with detailed neuropsychological testing evaluating patient's short-term memory and quality of life that at four months' time, which is a relevant point in time for anybody who unfortunately has developed brain metastasis, patients who had had a whole brain radiation therapy had worse problems with their memory, which would affect such important things as remembering to take medicines and obviously where did I put my cell phone, and they had a poorer quality of life than patients who had been treated with radiosurgery alone.

Foss So would not all patients want to go for the radiosurgery?

Knisely We think that it is a superior option. When we think about whole brain radiation therapy, that is a treatment technique that was developed in the 1960s and was used to treat patients who had developed large and symptomatic brain metastases, also that was developed at a time when we did not have effective systemic therapy for cancer. We now have the ability with MRI scanning and CAT scan to detect lesions when they are very small and we have a treatment technology that has made it very easy to pick off these very small marble and smaller sized spots in a single setting. We think we do a very good job at it, and we think it is a better option for treating patients.

Wilson Jonathan, with the accuracy that you are able to provide, does the gamma knife provide a higher

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dose of radiation to a lesion that a non-stereotactic, more traditional technique would be able to safely offer?

Knisely Yes, it does, because we are not including very much normal brain in the high-dose area, literally only a millimeter around the spot, maybe 2 mm, we are able to increase the dose significantly in that single setting. I have heard people refer to it as being radiocautery as opposed to radiotherapy, but if we are only treating the tumor, I think that we have very little downside to doing it that way.

Foss If a patient has had gamma knife, can they then go on to have whole brain radiation?

Knisely Yes, they can. The focal high-dose radiation does not preclude somebody receiving a whole brain radiation therapy in the future if that were required.

Wilson A question for both of you, can you discuss with our listeners what goes into the treatment planning process because obviously that is where the actual treatment plan is developed and is essential for the success of the treatment? What is involved with that? Jonathan, you had mentioned a PhD physicist as part of your team, how does it actually work?

Knisely The imaging studies that have been obtained on the patient on their morning of treatment are brought into a specialized computer workstation and we review those images with the physicist, identifying exactly where the lesions are we want to treat and setting up things that are called dose calculation matrices. Those are areas that we want to know the dose very accurately within. We will instruct the physicist, saying this is an area that we want to be very careful about, or if these are structures we do not want the radiation to hit to any significant degree, important things such as the optic nerves important for vision, or the cochlea, which is very important for helping you hear if we are treating a tumor very close to or involving the 8th cranial nerve, the hearing part of your cranial nerves, we will then let the physicist sit there and do his work, saying you are not doing it right, move it a little bit to the left, move it a little bit to the right, change it this way or that way. Once we have all agreed that we have achieved an optimized plan, then we print it out, we sign it, and push it on over to the treatment computer. It is relatively straightforward. This is, however, where I think the experience that we have allows us to be very comfortable with doing this because we do this literally five or six times a week. It is something that we do all the time and represents a major part of Dr. Chiang's and my practice. It is not something that we fire up once or twice a month, it is part of what we do to provide comprehensive services. We are fairly subspecialized.

Chiang I think that what comes with the Perfexion also is incredibly sophisticated software that was developed over the last 20 years that really allows the calculation for the doses that are required to be done in an almost seamless fashion. I certainly remember about 15 years ago when I was a resident that a lot of the calculations were part done by hand and all of that has really changed now and allows us to pretty much in real time do the calculations to what we need it to be.

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- Wilson You have both seen advantages in terms of efficiency and for the patients with the upgrade of the equipment.
- Chiang Very clearly, this is much more user friendly. It is much more comfortable from the patient perspective and the planning and treatment times have significantly decreased.
- Knisely One of the things that is important is that this machine has an increased, I guess, robotocization of the positioning that is required. If you had three spots in your head, for example, that we needed to move from the front left to the back right and then over all the way to the right above your right ear, we would need to go into the room and change your position manually with the previous version of the gamma knife, and perhaps change the diameters of the equipment that focuses the radiation on those spots, all that can be controlled automatically by a computer now, making it a lot more efficient for us to be able to offer treatment that is more complex to patients without having any time penalty. Everybody can still get out in time for dinner.
- Foss And the patient is awake through this procedure?
- Knisely Yes, no anesthesia, well, local anesthesia and a bit of sedation, but that is generally more for the MRI scan than for the actual treatment itself.
- Foss Do you see any advances in terms of thinking about combining other therapies with gamma knife, like what we talk about the use of radiation sensitizers in radiation oncology, do you foresee that there would be any direction that we might combine gamma knife with other agents or other therapies?
- Chiang From my perspective, what I have really seen more than the use of radiosensitizers or radioprotective agents, is how our tool can be used in combination in an interdisciplinary way. One of the groups that we work particularly closely with is the Melanoma Group and just our ability to understand how what we do interacts with the systemic agents that they administer and how far we can push the envelope as far as how long after radiosurgery these agents can be given and what would be helpful, I think, in the long run, would be to be able to look at each of the agents that each of these interdisciplinary groups uses and say you know what, it is safe to start this three days afterwards so you do not have to wait four or six weeks before you start chemotherapy or systemic therapy, and so those are the things that are starting to be developed as far as studies going forward.
- Wilson Jonathan, just jumping back to side effects for a minute, obviously with the whole brain treatment, I know patients can have hair loss with that, do you see hair loss with the gamma knife technique?
- Knisely We generally do not. Occasionally, if we are treating a lesion that is very close to the scalp, a very superficial meningioma, there might be a temporary focal loss of hair right over where the

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meningioma is located, but the high-dose radiation generally does not hit the skull or scalp, so there is no hair loss.

Foss And what kind of monitoring does a patient require after the therapy?

Chiang Once the head frame is taken off and vital signs, so blood pressure and heart rate are checked, and oxygen levels, if necessary, then there is actually very little monitoring that is required, it is the reason why it is an outpatient procedure, and people literally go right home once they get changed after their frame is removed.

Dr. Veronica Chiang is an Associate Professor of Neurosurgery and of Therapeutic Radiology, Director of Stereotactic Radiosurgery, and Medical Director of the Yale-New Haven Hospital Gamma Knife Center. Dr. Jonathan Knisely is an Associate Professor of Therapeutic Radiology and Co-Director of the Yale-New Haven Gamma Knife Center. If you have questions or would like to share your comments, visit YaleCancerCenter.org, where you can also subscribe to our podcast and find written transcripts of past programs. I am Bruce Barber and you are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.