Welcome to Yale Cancer Center Answers with your hosts doctors Francine Foss, Anees Chagpar and Steven Gore. Dr. Foss is a Professor of Medicine in the Section of Medical Oncology at Yale Cancer Center and she is an internationally recognized clinician and clinical researcher. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital at Yale-New Haven and Dr. Gore is Director of Hematological Malignancies at Smilow. Yale Cancer Center Answers features weekly conversations about the most recent advances in 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. May is Brain Tumor Awareness Month and this week you will hear a conversation about these tumors with Dr. Jennifer Moliterno Gunel. Dr. Moliterno is Assistant Professor of Neurosurgery at Yale School of Medicine. Here is Dr. Anees Chagpar.

Chagpar You recently joined Yale and you specialize in neurosurgery, particularly in the surgical treatment of brain tumors. Talk a little bit about what it is that you do and what makes your particular brand of brain surgery unique?

Moliterno As you know, I am trained as a general neurosurgeon here at Yale and while I was training, I really developed a passion for helping people with brain tumors and so I subsequently went to Memorial Sloan-Kettering for specialized fellowship training in the surgical treatment of brain tumors and spinal cord tumors, and in building my practice on my return here to Yale, I have really been focused on brain tumors primarily. I see all types of patients with all types of brain tumors whether it is primary, originating in the brain, or whether it secondary, meaning metastatic from other locations in the body, also benign tumors, malignant tumors, etc. And what really is special about it, I think, is the patient population. These are people who tend to be very scared when they get the diagnosis of a brain tumor, understandably so, and it is an honor and privilege to work with these people.

Gore Do you always know ahead of time before your surgery if it is going to be a benign tumor or a malignant tumor you are operating on?

Moliterno We have a very good idea based on MRI. There are certain characteristics that would suggest a tumor being benign versus malignant. Sometimes the location of the tumor helps as well, but we often have a good idea.

Chagpar Most people, and I respect the fact that you are a brain surgeon, think of it kind of like a rocket scientist, you have powers that most of us do

not, but for a lot of people we think of our brains as being vital structures that we do not particularly want somebody going in and taking big pieces out of, so how is it that you can take out a piece of somebody's brain and still have them be somewhat normal and functional afterwards?

Moliterno Very normal, and functional, and what I always tell my patients is that I am not doing this because I want to do this. I am not doing this because they want me to do this. This is something that we are both faced with. This is a situation where we have to intervene. And so typically what

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Gore How do people know or suspect they have a brain tumor, I mean that seems so scary?

Moliterno It is scary and you know people get worried too. I see patients all the time who have headaches that are completely unrelated.

Gore I cannot even remember the name of somebody I met yesterday. Should I be worried?

Moliterno Well, we can scan you. No, you know that is the whole trick with doing neurosurgical oncology, is knowing when a brain tumor is symptomatic and when the patient is symptomatic and usually by the time a patient gets to me we have established the diagnosis of a brain tumor and so whatever symptoms they have are likely related to the brain tumor, but of course patients will have headaches and headaches can be very, as you know, nondescript and a lot of people have headaches and they can be completely unrelated. The headaches that people usually get worried about, physicians usually get worried

about, is if there is a change in the type of headache that the personal usually has, if there is a change or if their headaches are worsening in terms of intensity or severity, frequency, just will not go away, that sort of thing, that is what prompts getting a workup. In addition, there can also be focal neurological deficits, that's what we call them that can be associated with tumors, so for instance if there is a tumor that is pushing on the eye nerve, the patient might present with vision loss or issues with visual acuity. If there is a tumor that is involving the motor aspects of the brain, they might present with weakness and so I think it is important, especially with signs and symptoms such as those, to seek medical attention.

Gore That sounds a lot like a stroke.

Moliterno Exactly, and more often than not, patients will go the emergency room or they will see their primary care doctor because they are concerned that they are having a stroke, and indeed it turns out that they actually have a brain tumor.

Chagpar Let's suppose somebody has a headache and they go and they see their doctor and the headache has been changing and they are worked up and low and behold they have a brain tumor. What strikes me about brain tumors is that it is housed within your skull. It is not something that you

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can feel. As a breast cancer surgeon, sometimes I can feel these cancers and I know where they are and if I do not know where they are, I can use imaging to find out where they are and take out the cancer. How do you exactly know where this thing is when you are in the operating room?

Moliterno We do a lot of leg work before we even get to the operating room, as you were saying, sometimes the patients will present with a headache or they present with what you mentioned, they cannot remember what they did yesterday or something like that, and so we have to then look at the imaging, see where the tumor is, and decide if they are related, is the patient symptomatic? Sometimes tumors can be found incidentally, but they could appear to be more malignant or they could be very large in size and then we will opt to do surgery regardless of whether or not they are symptomatic. We then do imaging and usually it just involves a regular MRI with and without contrast and it can help localize where the tumor is. Based on the location of the tumor, then

we can decide our operative plan and there are certain aspects that go into consideration. We can start out with something that is more minimal in terms of just getting a diagnosis, which would be a brain biopsy, which is usually reserved for cases of tumors that are located in very-very deep locations that are very difficult to access in that we would be concerned doing a larger surgery such as tumor removal that would result in problems for the patient. That is pretty rare though. The other aspect of it is there can sometimes be tumors that are located in more what we call eloquent areas of the brain and those are areas of the brain that are very important in function such as motor or speech and once we think that we are dealing with a tumor that is in one of those eloquent areas of the brain, we can get further studies and further imaging to help assess whether or not we can go ahead and resect the tumor as much as possible. That study that I am talking about is a functional MRI, which is a special MRI that shows us actually the function of the brain and the functional areas of the brain and it involves the patient interacting with the radiologist and a team during the actual MRI and then that imaging gives me information as to where the tumor is relative to those functional areas. And so it is not uncommon that the patients will see some surgeons that would be concerned that tumors would be near or within eloquent areas of the brain and offer a biopsy, but here at Yale we tend to be as aggressive as possible because the extent of tumor resection has been shown to be associated with improved outcomes.

Chagpar So you have to be as aggressive as possible without hurting those functional areas.

Moliterno Exactly, and that is what all the training is about, and sometimes what we need to do, and is one area of neurosurgery that I have really specialized in and focus on, is doing awake craniotomies, so when I see a patient who has a tumor that is in a very functional area, again speech or motor are typically the most common, sometimes we will need the patient to be awake during surgery, not the entire surgery, but part of the surgery. And part of deciding whether or not to do an awake craniotomy is really to know if it is necessary or not because it obviously can be very stressful for the patient, but we have protocols here to make it absolutely as comfortable as possible.

Gore So is it painful because they are awake?

10:47 into mp3 file http://yalecancercenter.org/podcasts/2014%200518%20YCC%20Answers%20-%20Dr%20Moliterno.mp3 Moliterno And that is what patients always ask, so again once we decide that it is indicated, and the reason that we do it again is to maximize the extent of resection but to make sure that we are maintaining the function that we want to preserve and so it is really not painful and it is

actually tolerated very very well. As I mentioned, we have a protocol here where we work with our neuroanesthesiologist and also our neuromonitoring staff and we put the patient to sleep in the beginning and do as I mentioned a craniotomy, which is our fancy way of saying that we make an incision and take off the bone temporarily and put it back at the end and while we are doing that bony work, the patient is asleep and the patient is under anesthesia just like any other circumstance, but the beauty with the drugs that we use now-a-days is that we are able to turn them off and the patient, within a few minutes, is able to wake up and we make sure that we use a certain amount of local anesthetics, so the patient is very comfortable and they are positioned in a comfortable way on the operating room table, and then the patient is able to interact with us during surgery.

Gore Wow.

Moliterno Once we expose the brain, we wake the patient back up and we start by stimulating the surface of the brain. For instance, if it is a tumor that is located in a speech area, we will ask them to start talking to us, or our neuromonitoring colleagues will do this part and they will ask them some tasks and some questions and get them talking and we will stimulate the brain. If we find an area of the brain that when it is stimulated causes speech arrest, that tells us that is an area we do not want to go into, because that is the area that leads to the production of speech and so it helps me then decide a better or safer trajectory to get to the tumor and that is usually in an area where I do not get responses like that. Once I get down and start resecting the tumor, what we usually do is keep the patient talking and so we ask them questions over and over again, or have them do verbal tasks or just interact with us, and while they are speaking, I am resecting the tumor, and so if there is ever concern, if the patient starts to slow their speech or they forget words or something like that, I stop immediately what I am doing and we give it some time and we see if it was a real problem that they were beginning to have and it allows us to push the extent of resection. It allows us to get as much tumor as is safely possible and it gives us real time feedback that the patient is going to maintain their function.

Chagpar That is very cool, being awake while your brain cancer is being taken out so that you can really push the forefront of taking out brain cancers. We are going to talk more about some of the cool stuff that Dr. Moliterno Gunel is doing with brain cancers right after we take a break for a medical minute. Please stay tuned to learn more information about brain cancer surgery with our guest Dr. Jennifer Moliterno Gunel.

Medical

Minute The American Cancer Society estimates that in 2014 there will be over 75,000 new cases of melanoma in this country with over 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. The patients with advanced melanoma have more hope than ever before. Each day patients are 14:46 into mp3 file http://yalecancercenter.org/podcasts/2014%200518%20YCC%20Answers%20-%20Dr%20Moliterno.mp3 surviving the disease due to increased access to advanced therapies and specialized care. 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 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 the focus on discovering the targets that will lead to improved 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 the WNPR Connecticut's Public Media Source for news and ideas.

Chagpar Welcome back to Yale Cancer Center Answers. This is Dr. Anees Chagpar and I am here with my co-host Dr. Steven Gore. Today we are joined by our guest Dr. Jennifer Moliterno Gunel and I am sure that those of you with us before the break remember how amazed I was and I am sure you were hearing about how Dr. Moliterno operates on patients while they are awake to take out their brain cancers, really enabling her to take out more cancer and preserve the functional areas. Jen, one of the questions I had was, all of that fancy imagining that you had before getting to the operating room, what about just using that in the operating room? Is that possible?

Moliterno Unfortunately it is not possible everywhere. We are very unique at Smilow Cancer Hospital that we have a 3-tesla MRI in our operating room and so it is the same type of MRI machine that they have in outpatient MRI facilities or in inpatient hospitals with the same resolution and the same imaging characteristics.

Gore Do you have to take them off the operating table and put them into that tube that people always complain about?

Moliterno So the tube, or the MRI machine, is actually housed in a garage and the garage is in the middle of two operating rooms. In one operating room, we have biplane angiography capabilities, which is just a fancy way of saying we

are able to do angiograms or look at the blood vessels from the inside and the two of those together really give us endless possibilities in terms of neurosurgery and we are the only center, to my knowledge, in New York and New England area that has both the biplane angiography and 3-tesla MRI in the operating room. The other operating room only has access to the MRI but the MRI is able to swing back and forth between both rooms and so typically, and this is with the patient asleep or awake, either one, I will do the surgery and being a brain tumor surgeon much of, as you probably know, resecting the tumor is by feel and by sight and so you can really tell what is tumor and what is brain and you can feel that as well. However, with certain types of brain tumors, they can be very infiltrative into the brain and so even under the microscope, even being a primary brain tumor surgeon, it can still be difficult to tell what is normal brain and what is tumor and that is where the MRI really helps. So once I get to the point

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that I think I have gotten the majority of the tumor out, we then bring in the MRI. We give the patient some dye, which takes about 35 minutes or so, and we can get a full series of images. We then will look at the imaging, see what, if anything, is left in terms of tumor. If it seems that it is in a safe area that I can resect then we will register that MRI to a navigation system, which is kind of like a GPS and then I can go back into the surgery and pinpoint exactly where that tumor is left. Even though it might look like regular brain.

Gore Using the GPS?

Moliterno We use that GPS from the start in most of our surgeries.

Gore It is not on your cell phone I am assuming?

Moliterno No.

Chagpar One question that I have is, with the dye that you are talking about, with the MRI, often times that dye is in the blood vessels and you can get a blush with open blood vessels, which tend to occur with surgery. So how can you tell the difference between just a little bit of oozing from open blood vessels versus residual cancer?

Moliterno Usually we can tell by comparing the different series and so usually if we compare before the dye is given, we always take a series an MRI series, and then we give the dye and then we take another type of series and we actually have the capabilities of subtracting the blood vessels or the blood essentially away and so whatever the residual enhancement is or the residual dye that we are seeing is tumor.

Gore It sounds like this is very complicated and long surgery?

Moliterno No, as I said the MRI will add on probably about 35 or 45 minutes, something like that because of course we need to do accounts and make sure that the patient is safe to bring the MRI and that sort of thing, but typically for run of the mill brain tumor it usually takes us just a few hours.

Chagpar A lot of our listeners who have ever been in an MRI know that you cannot have any metal in the MRI, you do not take your credit cards in the MRI, but people who have been in an operating room also know that there is a lot of metal that surgeons use. So people may be wondering how exactly is it that you operate in a circumstance where there is an MRI without getting all of your metal instruments in the way?

Moliterno That is why the MRI is housed in the garage and so it only comes out when we want it to but there are signs everywhere that says the MRI is always on and it is always on and we always have to be cognoscente of that. We have safety officers actually that are standing outside the MRI rooms

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all the time guarding the rooms and checking everybody for metal going in and out and then of course the metal that is in the room, as you were saying, the surgical instruments, we keep those sterile during the interaoperative MRI and so they are just off to the side covered in sterile sheets but outside of the line, which allows it to be safe and in terms of anesthesia they use nonmetal machines, instruments and that sort of thing.

Gore How soon after the surgery do you know how good the neurologic recovery is going to be for the patient?

Moliterno Usually it depends on the case and it depends where we are working. If we are working in quite areas of the brain, usually we expect that the patient will wake up just fine. If we are working in more eloquent areas of the brain, as I mentioned near motor or speech, there can always be swelling associated with surgery, but we get a pretty good gauge when the patient wakes up right there in the operating room and of course, sometimes the patient does have a little bit of swelling after surgery that may worsen function temporarily, but how they wake up initially is usually a very good gauge.

Gore Is this kind of surgery usually the end of the story for the patient's treatment or do they have to interact more with radiation doctors or medical oncologists as well?

Moliterno This is usually just the start depending of course on the type of tumor, but we usually start out with an aggressive surgery and then we continue with aggressive management of certain types of brain tumor. We have a multidisciplinary tumor board that meets weekly with all physicians and then other staff of course dedicated to the treatment of brain tumors or neurosurgeons such as myself and medical neuro-oncologists, radiation oncologists, neuro-pathologists, neuro-radiologists and we all come together and we discuss all the patient's that we treat. I will describe the surgery, what I found, what I was able to accomplish. We will review the pathology and then we will make a treatment plan going from there. Of course part of this is standard of care. So for most tumors there is standard therapy that we give following surgery, but for other stages there are exciting clinical trials that can be offered and we are really on the forefront of offering these clinical trials here at Yale.

Chagpar One of the questions that people always ask, and perhaps it is less of a question but more of a statement, is that they are afraid of clinical trials and they say things like, I do not want to be a human guinea pig. I do not want to have human experimentation, and yet so many of our guests say that clinical trials are on the forefront and that people do better on clinical trials than they would if they were not on a clinical trial. Can you talk a little bit about clinical trials and how important they are for patients and whether or not patients should actually sign up for these.

Moliterno I think that it is very important for patients again to understand that they are not being used as guinea pigs. This is just looking for ways to tackle a difficult to treat tumor and again this is not with regards to all types of brain tumors. This is with the more malignant types that we are talking

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about and again there is often a standard of care and even with brain cancer there is a standard of care but the clinical trials give different approaches or newer approaches to tackling when these tumors progress or when they recur. Sometimes the trials can also be offered upfront, meaning along with standard of care. But I think that it is very important to meet with the doctors, the neuro-oncologists, the people who run the clinical trials and understand what exactly the trial is and how it is going after the tumor because they can be very effective.

Gore Does this tend to be kind of one size fits all based on tumor type A, looks like other tumor type A's that you have seen, or other specialized test that can be done that can separate different patients and how their tumors may be?

Moliterno Absolutely, so there is of course the variability amongst different types of brain tumors which is quite significant and then even when we get into certain tumors, again the malignant types of brain tumors in particular, there is such heterogeneity, there is such difference amongst one tumor compared to the other and usually at a genetic level and mutational level within the tumor itself. Another thing that we are doing here at Yale with the Yale Genome Project is sequencing these tumors and understanding the genetic mutations that are underlying and that is one reason why certain drugs may not be effective in certain people but effective in other people, and so ideally the goal will be to develop a more personalized therapeutic rationale in targeting those underlying mutations or the things that have gone in tumors and then having a more individualized therapy.

Chagpar What you are talking about is genetically sequencing the tumor itself. Is there any concept of genetically testing individuals who may be predisposed to getting brain cancers just like there are individuals who are at increased risk of developing breast cancer or ovarian cancer?

Moliterno There are some syndromes, they are rare and very uncommon, not like with breast cancer where there are higher pre-dispositions for having brain tumors, but they are very uncommon. Unfortunately it just seems that there are genetic issues or mutations within the tumors themselves and randomly happen in people.

Chagpar Earlier in our discussion you made a distinction between primary brain cancers and secondary brain cancers and I would think the genomic characteristics of those is different, is the treatment paradigm different as well? Is it the same thing to resect a cancer that came from the brain itself versus one that came from another part of the body?

Moliterno Yes, they are very different. The paradigms are different. The surgery even itself is different. The primary brain tumors tend to be more infiltrative throughout the normal brain whereas the metastatic tumors or secondary tumors tend to be more encapsulated, if you will, and in terms of the treatment it is very different, the primary brain tumors rarely if ever, I would even say never

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metastasize outside of the brain and so it is really just dealing with the brain cancer itself and using certain drugs that are targeting that particular brain tumor whereas, for metastatic disease we are looking more towards treating systemically.

Dr. Jennifer Moliterno Gunel is Assistant Professor of Neurosurgery at Yale School of Medicine. We invite you to share your questions and comments with the doctors. You can send them to canceranswers@yale.edu or leave a voice mail message at 888-234-4YCC. As an additional resource archived programs from 2006 through the present are available in both audio and written versions at yalecancercenter.org. I am Bruce Barber hoping he 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.