

Dr. Joseph Piepmeier, Surgical Treatment Options for Brain Tumors April 6 , 2008

Welcome to the Yale Cancer Center Answers with Drs. Ed Chu and Ken Miller. I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center and Dr. Miller is a Medical Oncologist specializing in pain and palliative care. He also serves as Director of the Connecticut Challenge Survivorship Clinic. If you would like to join the discussion you can contact the doctors directly. The address is [canceranswers@yale.edu](mailto:canceranswers@yale.edu) and the phone number is 888-234-4YCC. This evening, Dr. Miller speaks with Dr. Joseph Piepmeier. Dr. Piepmeier is Nixdorff/German Professor of Neurosurgery at Yale School of Medicine.

There are basically two types of brain tumors, tumors that arise within the brain called primary brain tumors, and secondary brain tumors which are metastatic lesions or cancers that arise somewhere else in the body and then deposit tumors in the brain.

Miller Are all tumors that arise in the brain cancerous, or are some of them benign?

Piepmeier Most of the patients I see have a malignant disease, but the World Health Organization calls all gliomas malignant. This really is not helpful because gliomas are primarily classified as either high grade or low-grade lesions, and there is a very different biology between those two groups. The high-grade lesions, unfortunately, are far more common than low-grade tumors, but there are a variety of benign lesions that arise from the nerves, or the covering of the brain called meninges, and these are also classified as brain tumors.

Miller That would be meningioma, and that is usually not a cancer.

Piepmeier Correct.

Miller How common are tumors that arise in the brain, a glioma for example?

Piepmeier The incidence is probably somewhere between 13,000 and 15,000 cases in the United States annually, so it is not common as other forms of cancer.

Miller Do we know why this is?

People have been talking about cell phones for example.

Piepmeier There is no evidence that cell phones have a relationship to the evolution of these tumors. The only known causative factor is exposure to ionized radiation at primarily a young age. Aside from that there are really no other known causes. We do know that all cancers are the result of genetic mutations and there is a lot of work being done establishing how that

2:28 into mp3 file [http://www.yalecancercenter.org/podcast/Answers\\_Apr-6-08.mp3](http://www.yalecancercenter.org/podcast/Answers_Apr-6-08.mp3) relates to the evolution of brain tumors, but in terms of the causative factor, we do not know.

Miller Are they becoming more common?

Piepmeier As the population ages and with the improved ability to diagnose and access to imaging, the frequency probably is increasing.

Miller For a patient who has a brain tumor, typically what do they come to the doctor complaining of, how would they know that there is something wrong?

Piepmeier The most common symptoms are progressive headaches, new onset of seizure activity or a progression of a neurologic problem such as weakness, numbness, memory change or vision change, and this typically progresses over days to weeks.

Miller Lots of people get headaches, how would these be different than just the regular headache or a migraine headache which people talk about a lot.

Piepmeier Sometimes you cannot tell the difference, but what we are noticing is that these headaches are very different than headaches the patient may have routinely. They commonly

do not respond to over the counter medications. Very classically they are worse in the morning when the patient awakens and get better during the day. That constellation of a headache would be sufficient for the patient to consult with their physician. Miller So mainly if it persists? Piepmeier Correct. Miller If a patient goes to the doctor and they have experienced a new onset of seizures, or this different type of headache, what would typically happen then? Piepmeier We would examine the patient to see if there is any neurologic problem to correlate with the symptoms. If that were the case, this would lead us to think there may be a structural lesion in the brain. Then that would be someone who should proceed to some diagnostic imaging. Miller At this point, what is state-of-the-art in terms of imaging, as a neurosurgeon what would you choose? 4:37 into mp3 file [http://www.yalecancercenter.org/podcast/Answers\\_Apr-6-08.mp3](http://www.yalecancercenter.org/podcast/Answers_Apr-6-08.mp3) Piepmeier The best anatomic detail and resolution is clearly an MRI. The quality of imaging and the degree of information you can gain from that sequence of imaging is very important. It is really the gold standard in terms of evaluating the brain tumor. Miller You and I were talking before the show about how long we both have been involved with Yale. If we went back to the beginning of your career, what was available, in comparison, for someone with a brain tumor? What would have helped you make the diagnosis at that point? Piepmeier Fortunately my career started when we had the old ACTA scan, which was an ancient machine that took black and white Polaroid pictures of the brain. They were not very informative, but preceding that it was a matter of examination and arteriography and even pneumoencephalography, which were very poor surrogates for brain imaging. Miller How has that changed your approach in terms of surgery, are more people operable, less people operable; how do you make that decision? Piepmeier Tumor location is the primary indicator as to whether or not this is something that has to be removed, but there is a lot of information on additional imaging strategies such as what is called a functional MRI where you actually map out specific cortical regions in the brain that activate with certain activities. Then, based on the knowledge of neuro anatomy, you can anticipate what the potential neurological problems are that might occur with surgical removal of the tumor. All of that is incorporated into making a decision about whether or not the patient will have an operation. Miller Let us go back to a functional MRI because I know very little bit about it. What does it mean and how do they do a functional MRI? Piepmeier Basically this is a technique with an MRI machine where you can measure increase blood oxygen demand, and when you activate a certain area of the brain, such as with movement of your hand, that area of the MRI that is primarily mediating that activity gets an increased blood supply. That increased blood supply can be detected by an MRI, so you can delineate on a specific cortical region that area of the brain that mediates that function. Important activity such as motor function, language or even vision, are things that can be anatomically located within the brain on an MRI prior to surgery. 7:30 into mp3 file [http://www.yalecancercenter.org/podcast/Answers\\_Apr-6-08.mp3](http://www.yalecancercenter.org/podcast/Answers_Apr-6-08.mp3) Miller It sounds like you can predict before surgery, what impairment the patient may have with surgery, is that correct? Piepmeier You can make an estimation,

yes. There is no such thing as the procedure without risk, but you can minimize that risk by knowing the anatomy and knowing the localization and infiltrative nature of the tumor prior to surgery. Miller You are looking at an MRI scan and you've got someone with new onset seizures, different headaches and they have a mass in the brain and you need to find out what it is. How do you do a biopsy of a brain tumor? Piepmeier One of the important factors of the MRI scan is that they are very, very good at showing us abnormalities, but in general they are not very good at telling us what the abnormalities are; they are not specific enough to make a diagnosis with most primary brain tumors. In order to render a diagnosis, you need a biopsy which is a procedure that can be done through a small opening by passing a probe into the target region and sending that to the pathologist for an answer. We do these with what is called frameless stereotaxis, which means we can actually use facial features of the patient to render precise localization through a computer in the operating room that demonstrates a probe going precisely to the target at the time of surgery. This way, the surgeon knows he is biopsying the precise area that he wants. Miller As the surgeon are you guiding the biopsy probes done or is the computer? How do you do it? Piepmeier The surgeon is guiding and doing the surgery, but you get visualization in three dimension of that probe passing through the imaging study at the time of the operation. Miller It sounds amazing. Piepmeier It is a nice way to do surgery and it has a degree of safety ensured. Miller When you have made a diagnosis, you then have to discuss about whether to operate or not. What are the factors that you consider before you make that final decision? Piepmeier Risk is the ultimate decision making issue. In general, it is fairly well accepted that when reducing the amount of tumor that is present when a patient has to move on to other forms of treatment, such as radiation, 10:06 into mp3 file [http://www.yalecancercenter.org/podcast/Answers\\_Apr-6-08.mp3](http://www.yalecancercenter.org/podcast/Answers_Apr-6-08.mp3) chemotherapy, that cytoreduction has benefit in terms of improving the efficiency of those next steps in treatment. Miller In terms of risk, it would be loss of function, or potentially loss of life. Piepmeier It is extraordinarily rare that a patient would die from one of these operations, but it is the impact on the patient's capacity to function that is the primary factor that dictates how aggressive you can be with surgery. Miller We have an email from one of our listeners asking about gamma knife. Piepmeier Gamma knife is a technology that can highly focus high dose radiation to discrete targets. It has been a wonderful tool for the treatment of patients, primarily with metastatic disease. Some benign brain tumors were also good candidates for this treatment, but for the vast majority of patients with gliomas, these were not well-demarcated focal targets. They are diffuse and infiltrative tumors and gamma knife is a wonderful tool, but not very helpful with the majority of patients with primary brain tumors or gliomas. Miller So for those patients you would generally lean towards surgery as opposed to radiation? Piepmeier Those patients typically would have surgery and in the high-grade population, these patients would then move on to external beam radiation treatment. Miller We would like to remind you that you can email your questions to us at

canceranswers@yale.edu. We are going to take a short break for a medical minute. Please stay tuned to learn more about the treatment of brain tumors with Dr. Joseph Piepmeier from the Yale Cancer Center. 12:37into mp3file [http://www.yalecancercenter.org/podcast/Answers\\_Apr-6-08.mp3](http://www.yalecancercenter.org/podcast/Answers_Apr-6-08.mp3)Miller Welcome back to Yale Cancer Center Answers. This is Dr. Ken Miller. I am here with Dr. Joseph Piepmeier, who is the Professor of Neurosurgery at Yale School of Medicine and the Yale Cancer Center. Joe, we are talking about the symptoms of brain tumors and how you make a diagnosis. We started talking about surgery and radiation. If someone has had a resection, if you have removed a brain tumor, what is the typical recovery like for that patient? How long will they be in the hospital and what happens next?Piepmeier The patient is usually in the hospital about 3 or 4 days and when they go home they are typically independent in their activities, but restricted for a couple of weeks. At that time, we will start the next steps of treatment.Miller Let's get right into that. You have removed the tumor, and years ago with a lot of other types of tumors, the surgeon would say I got it all and that is all you need to do. Is that case with neurosurgery?Piepmeier It is not the case with gliomas. We know that these are tumors that are not well demarcated from the surrounding brain, so the surgical target is that part of the tumor which is identifiable as solid tumor tissue. The portion of the tumor that infiltrates into the brain around that original tumor, is not a surgical target. That is the portion of the tumor that radiation therapy and chemotherapy treat.Miller The patient has recovered and they go to the radiation oncologist, how do they target the area and what do they do?Piepmeier Fortunately we work as a collaborative multidisciplinary unit at our institution and so decisions about the treatment are made in consultation with a neurosurgeon, a neurooncologist, the radiation oncologist, the medical oncologist, the neuro pathologist and the neuro radiologist. All of this material is reviewed on each patient. The decision about what type of radiation or what type of chemotherapy, is basically derived from input from all of those disciplines, but traditional radiation therapy is given in daily fractions; typically 5 days a week for up to 6 weeks. That dose symmetry planning enables you to focus radiation on the tumor to try to kill those tumor cells and yet spare injury from the surrounding brain.Miller In terms of chemotherapy, is there a role for chemotherapy in trying to reduce the risk of the cancer coming back?Piepmeier Absolutely, and the standard of care right now is the drug temozolomide, which is an oral agent that is taken in low doses during radiation. Once15:21into mp3file [http://www.yalecancercenter.org/podcast/Answers\\_Apr-6-08.mp3](http://www.yalecancercenter.org/podcast/Answers_Apr-6-08.mp3)radiation is completed, it is given in cycles with a higher dose. These are a series of pills that patients can take. They do not cause the side effects that used to characterize chemotherapy in the past. Most of these patients can take this medicine and go to work.Miller I was going to ask about that. There is a common misperception among patients that they will have a lot of side effects and if they don't, they think it's not effective.Piepmeier It is very effective and we are seeing some very nice responses to it, but even more than that, now we are finding that because there are specific genetic defects that relate to the

evolution of these tumors, these genetic defects turn off the cells ability to stop proliferation. We are now able to identify those pathways and target therapies in directly to address the signaling problems in those pathways to help control the tumor. Miller It is essentially targeted therapy, which is being used a lot in oncology. I know you are doing work on convention enhanced delivery chemotherapy, what does that mean? Piepmeier This is a new technique where you can actually place a small catheter in the brain and directly infuse the chemotherapy or the targeted treatment directly in the brain where those infiltrative tumor cells reside. By selecting an agent to infuse, it attacks only the tumor cells. You can selectively control the tumor and not injure the surrounding brain tissue. Miller So the tumor cells that are left in that area will actively take up the chemotherapy. Piepmeier Correct. Miller How do you choose drugs that have fewer side effects in terms of normal tissue? Piepmeier One of the ways is to try to select a specific target that is present on the tumor cells and not on the normal brain tissue. There is a receptor for epidermal growth factor, a mutative receptor called EJFRV3, which is present in about half the malignant primary brain tumors and by targeting that specific receptor with an antibody, you can actually direct therapy toward the tumor cells and spare the brain. Miller If you gave the same drugs intravenously, as we do for treatment of other types of cancer, would they get into a brain tumor? 17:55 into mp3 file [http://www.yalecancercenter.org/podcast/Answers\\_Apr-6-08.mp3](http://www.yalecancercenter.org/podcast/Answers_Apr-6-08.mp3) Piepmeier To a certain extent they would and intravenous is still a viable option. It has the benefit of being distributed to the blood system, to having access to wide areas. It is the ability of that compound to pass from the blood vessel into the brain that remains to be a challenge. The benefit of the convention delivery strategy is you obviate that blood brain barrier obstruction by putting the agent directly into the spot or site where you need it. Miller What else is new in terms of cutting edge therapy? Tell me about using viruses, how would you do that? Piepmeier This is a very interesting strategy that we have developed in the neurosurgery laboratories with Tony Vandemore. We have developed a virus, which is a variant of vesicular stomatitis virus, which has been developed to directly attack tumor cells and not normal brain tissue. This is a replication competent virus, which means that once it gains access to the tumor cell, it can actually replicate and go to the next tumor cell. There has been some fairly remarkable laboratory work both in the Petri dish and in the research animal, showing that this virus directly attacks the tumor and does not attack the brain. It is very exciting work. Miller The next step is bringing this to people; is there some trepidation with that, or is there confidence that this really may be a breakthrough? Piepmeier I think the strategy may be a breakthrough, whether or not this virus is the ultimate agent used is unknown. Our primary concern is not only its ability to kill the tumor cell, but to protect the patient, so additional work needs to be done to make sure this virus, or some variant of this virus, is safe so the treatment itself does not make the patient sick. Miller If a patient or a family member is listening to this and wants to learn more about what is available in terms of clinical trials here at Yale, how would they get involved? Piepmeier It is very easy to get involved. We are certainly on the

Yale Cancer Center website and there is a Yale Brain Tumor Center website. There is also a phone number, 203-785-2791, where Betsy D' Andrea, who is the clinical coordinator, will be happy to take information and make arrangements for the patient to be seen. We are dedicated to seeing patients rapidly and typically we can see new patients within the same week. Miller At that point they would perhaps be seen by yourself, but also by the20:44into mp3file [http://www.yalecancercenter.org/podcast/Answers\\_Apr-6-08.mp3](http://www.yalecancercenter.org/podcast/Answers_Apr-6-08.mp3)entire team of people and different specialists that you mentioned before. It sounds like a strategy is mapped out. Piepmeier That is correct. We believe that this collaborative relationship in bringing multiple disciplines to the table for each patient enhances the quality of healthcare. Miller We received an email question from a woman in Southington. She was asking about drugs that are involved with angiogenesis, which is the development of blood vessels, and how that property of angiogenesis comes into play with brain tumors and how you are targeting that? Piepmeier Angiogenesis is a very robust part of primary malignant brain tumors and it is a viable target for therapy. Developing strategies specifically focused on this are an ongoing interest. We have seen some fairly remarkable responses to the use of the current drug Vevasystemac. It has been recently FDA approved for the treatment of breast cancer. It has also been used to treat primary malignant brain tumors and we see this as a significant benefit in some patients in terms of controlling their tumor. Miller It is a fascinating thing that some of the drugs that are approved for one indication such as for breast cancer, can have activity in tumors that are very, very different. Piepmeier Absolutely and that is one of the reasons why, especially with many solid tumors, advances in one area can be adopted in other disciplines and other types of cancer. Miller People talk about the concept of bench to bedside, what does that mean in terms of Yale and brain tumor research? Piepmeier That is a very active process at our institution and we have dedicated science and research personnel that are actively working on these problems, not only in our own department of neurosurgery, but also in the Department of Biomedical Engineering and the other disciplines within the hospital. We have a new research project that will be starting this spring, which will be dedicated toward adapting convention-enhanced delivery of targeted therapies that attack cancers stem cells. We feel that these are likely the most resistant form of cancer within primary malignant brain tumors, and if we can target those cells specifically, we are going to be much more effective in terms of treatment.23:24into mp3file [http://www.yalecancercenter.org/podcast/Answers\\_Apr-6-08.mp3](http://www.yalecancercenter.org/podcast/Answers_Apr-6-08.mp3)Miller It is an important term you just brought up. What are cancer stem cells and how are they different than the cancer itself? Piepmeier The identification of the stem cells is probably the most important discovery in the history of medicine. These are cells that reside within the adult human brain that maintain the capacity to produce other more mature forms of cells. We also think that these pluripotent cells are the cells of origin for brain tumors. The ability for these cells to migrate within the brain and to go to different regions, also characterizes the same problems that we see with primary brain tumors. New evidence shows that of all the forms of therapy we use, the

most resistant cells appeared to be a subpopulation of cancer stem cells. Our strategy is, if that really is the cause of resistance, then we need to focus on that subpopulation within the cancer. We are dedicating an entire research project to this. Miller I shouldn't say easier, but the slightly easier cells to get rid of are the more mature tumor cells that were used to seeing. You are saying that there is actually a population of cells that are more primordial, more primitive than that? Piepmeier That is a very important concept that is relatively new. There are a number of ways to try to identify what a stem cell is within a brain tumor and that still remains to be defined. Apparently, there are several different markers that can be used, but I think the research data is pretty clear that if you take that population of cells out of a malignant tumor and study those in a laboratory, they have much more aggressive behavior than the other more mature cells that were within the tumor. Miller So in a sense the goal of treating someone with a brain tumor is with surgery to remove the bulk of the tumor, and then the second goal is to remove any other mature tumor cells. What you are really saying is probably the toughest goal right now is getting rid of the stem cells. Piepmeier That appears to be the case. Miller Anything else you want to share with us in terms of advances in surgery, surgical techniques or advances in research that you are excited about? Piepmeier One of the important things about the new Smilow Cancer Hospital at Yale is that we are going to incorporate a high intensity MRI unit within the operating room. This will enable us to do more precise, detailed surgery and more aggressive surgery in the treatment of a variety of disorders including brain tumors. The other thing that we have, along with 26:20 into mp3 file [http://www.yalecancercenter.org/podcast/Answers\\_Apr-6-08.mp3](http://www.yalecancercenter.org/podcast/Answers_Apr-6-08.mp3) the multidisciplinary approach, is that the nurse coordinator, Betsy D' Andrea has a patient, family support group that meets monthly. We feel this is also a very valuable asset in terms of patients and families dealing with cancer, especially cancer in the brain. Miller I want to thank you Dr. Joseph Piepmeier for joining us. Piepmeier It was great, thank you. Miller It has been wonderful hosting you on Yale Cancer Center Answers today. Until next week, this is Dr. Ken Miller at Yale Cancer Center wishing you a safe and healthy week. If you have questions, comments, or would like to subscribe to our podcast, go to [yalecancercenter.org](http://yalecancercenter.org) where you will also find transcripts of past broadcasts in written form. Next week, we will learn about the treatment of childhood cancer with Dr. Gary Kupfer