

Dr. Jill Lacy, New Hope for Patients with CNS Tumors April 26, 2009 Welcome to Yale Cancer Center Answers with Dr. Ed Chu and Francine Foss, I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center and he is an internationally recognized expert on colorectal cancer. Dr. Foss is a Professor of Medical Oncology and Dermatology and she is an expert in the treatment of lymphomas. If you would like to join the discussion, you can contact the doctors directly. The address is canceranswers@yale.edu and the phone number is 1888-234-4YCC. This evening we welcome Dr. Jill Lacy. Dr. Lacy is an Associate Professor of Medical Oncology at Yale Cancer Center specializing in the treatment of brain and spinal cord tumors. Chu Jill, let's start off by discussing what tumors of the central nervous system are. Lacy Well, the definition of a tumor of the central nervous system is an abnormal growth of cells within the brain or the spinal cord, or within the tissues that cover the brain. Basically, there are two types of brain tumors that we talk about, primary brain tumors and metastatic brain tumors. Foss What is a metastatic brain tumor? Lacy That's a tumor that begins as a cancer elsewhere in the body, outside of the brain, and then spreads to the brain where it can grow either as a solitary single tumor mass, or in some cases as multiple small discrete tumor masses within the brain. For example, lung, breast, kidney, and melanoma are the cancers that frequently metastasize to the brain, and lung and breast are the most common types of metastatic brain tumors. Foss How common is brain cancer and at what age do patients generally come down with brain tumors? Lacy Metastatic brain tumors are quite common. There are about 150,000 new cases of metastatic brain tumors diagnosed each year. Turning to primary brain tumors, these are tumors that arise in brain tissue and grow within the central nervous system. They can diffusely infiltrate the brain and spinal cord, but they rarely spread or metastasize outside of the CNS to other sites in the body. What can be a little confusing for patients, and even in some cases for physicians, is that there are many different types of primary brain tumors. There are at least 15 by the current classification system and they all have a somewhat different biology, natural history, prognosis, and treatment. Some of these primary brain tumors are truly benign and others are malignant. 2:40 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Apr-26-09.mp3 Chu What would be the primary CNS tumor that we should be most aware of, especially for the adult population, which type? Lacy Well let's backtrack a little bit. Brain tumors are classified by pathologists based on the type of cell from which they arise. The most common type of primary brain tumor is called a glioma. A glioma is a brain tumor that arises from glial cells, and these are the cells in the brain that form that kind of spongy material that supports the brain nerve cells or neurons, and more than half of primary brain tumors are gliomas. There are actually several different subtypes of gliomas, and they run the spectrum from being indolent low-grade benign tumors to very malignant, highly aggressive tumors. The most common type of brain tumor overall is the highly malignant variant of glioma called glioblastoma multiforme. Chu Are there any risk factors that have been identified, say for

this most aggressive form of brain cancer, glioblastoma multiforme, that is also known as GBM?

Lacy Who gets brain tumors? What are the risk factors? There have been a number of studies looking at potential environmental factors that can cause brain tumors. In fact, there have been hundreds if not thousands of these studies looking at things like petrochemicals, dietary components, power lines, cell phones, and none of these studies have really shown any substantive link to the development of brain tumors, which is somewhat reassuring. The only clearly defined risk factor for primary brain tumors is ionizing radiation, or x-rays, and this link comes primarily from treatment of children with leukemia who get brain radiation to prevent relapse in the brain. We know from that data that radiating the brain is associated with about a ten fold increased risk for a benign type of tumor called meningioma, and about a sixth fold increase in risk of gliomas, which sometimes can be malignant. Given the link with x-rays, there is some concern about unnecessary radiation of the brain, and this concern has been raised, for example, with dental x-rays. Now, dental x-rays involve a very low dose of radiation and so far there is no clear link to brain tumors with judicious use of dental x-rays in the general population.

Foss What are signs and symptoms of a brain tumor?

Lacy There are patients who present with focal neurologic symptoms, headaches, or seizures. The focal neurologic symptoms can be quite varied depending on the location of the tumor within the brain. For example, a patient may present with several weeks of right-sided weakness, reflecting a tumor in the left side of the brain, they may present with difficulty speaking, which is reflective of a tumor in the language center of the brain, or with visual abnormalities, reflective of a tumor in the vision center or occipital lobes of the brain.

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Typically, these focal neurological symptoms are progressive over weeks or months. They usually are not sudden in onset and in fact we are often taught in medical school that the sudden onset of focal neurologic symptoms, in general, is indicative of a stroke rather than a brain tumor.

Foss You talked about headaches. Can you reassure our listeners a little bit about headaches, because we all have them so when do we worry about a headache as potentially being a brain tumor?

Lacy Good question. About half of the patients who are ultimately diagnosed with a brain tumor will complain of headache. There is no clear pattern of headache associated with brain tumors. They can be mild or severe. In some cases they are quite severe and associated with nausea and vomiting, which can be indicative of an increase in pressure in the brain from the mass of the tumor. Now headaches are obviously very common and we all experience them often on a regular basis, and the overwhelming majority of people who experience headaches obviously do not have brain tumors. But, if you are experiencing headaches for the first time, headaches that are more severe than the usual pattern or increase in severity and frequency, it's always wise to check in with your health care provider.

Chu So say if the headaches are different than normal, or any of the other symptoms that you had mentioned should arise, who should they go to? Should an individual see their primary care physician? Should they see the neurologist? Should they come and see you,

the medical oncologist? And then what needs to be done subsequently?Lacy Seeing your primary care provider is often the first place to start, and then they can refer you on if it's necessary.Foss What is the treatment for brain tumors? You have talked about a number of different types, and I am sure there is a whole bunch of different ways of approaching them, but can you give us just a general overview of the treatment approach?Lacy Treatment of brain tumors is very interdisciplinary and involves primarily three modalities; surgery to remove the tumor or get a biopsy, radiation therapy either as the primary treatment or as an adjuvant to surgery, and chemotherapy or drugs are used to treat brain tumors. The primary treatment generally is considered surgical resection, and for benign tumors that often is curative, for malignant tumors it will relieve mass effect and symptoms and has been associated with a better survival. However, not all brain tumors can be removed surgically. If they are located deep in the brain, if they are located in a critical site within the brain, or if9:02 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Apr-26-09.mp3 the tumor is very extensive, it's not possible to remove the tumor surgically. The alternative in that case would be either radiation or something called radiosurgery.Foss You talk about brain tumors as being solitary lesions, and we use the word metastasized for other kinds of cancers. Could you clarify for our listeners, do brain tumors spread to other parts of the brain and do they spread outside of the brain?Lacy This relates in part to a question that patients often ask when they are first diagnosed with a brain tumor, is this tumor malignant? Is it cancerous, or is it benign? Because outside of the brain that's obviously a very important distinction. Malignant tumors in the brain are aggressive and they can diffusely infiltrate the brain and even the spinal cord and they grow rapidly. They are life threatening and in most cases eventually they will recur and are often fatal. Interestingly, they rarely metastasize outside of the brain and the spinal cord, outside of the CNS. Benign tumors by contrast grow very slowly. They can be present for years with no growth. They tend to be well demarcated within the brain, they don't diffusely infiltrate the brain and they often are associated with a very long natural history and may not need treatment. Where it can be confusing in the brain when we are dealing with primary brain tumors is that benign tumors can present with the same types of symptoms that malignant tumors present with and patients often are living with significant neurologic deficits from benign tumors. Benign tumors are also treated with the same modalities that we use to treat malignant tumors; surgery, radiation, and less often drugs. Benign tumors, if progressive, can in some cases rarely be fatal. The other issue is that benign tumors sometimes have the potential to become malignant, and by that I mean that they can recur after they have been treated, they can recur multiple times, and in some cases they can actually transform and become a malignant or aggressive tumor. The distinction between benign and malignant tumors in the brain can sometimes be a challenge both for the patients and the physicians.Chu The help to distinguish between benign and malignant, can that be done solely on imaging such as a CT or an MRI, or does a more invasive procedure need to be done?Lacy The way we define a tumor in

terms of the subtype and whether it's malignant or benign is done using two modalities. The first is imaging, brain imaging, and most patients who are diagnosed with a brain tumor will get a CAT scan or an MRI scan that will show the tumor within the brain. Now, if they have had a CAT scan they should get an MRI scan because it's a much more sensitive test. It also gives us a lot of information about the type of tumor that we are dealing with based on these characteristics; does it take up the dye that's injected when the study is done and are there multiple lesions? Often times, from the MRI scan alone, 12:22 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Apr-26-09.mp3 we have a pretty good idea as to whether we are dealing with a benign tumor or a malignant tumor. Ultimately, of course, we want to get tissue to look at under the microscope and the pathologists can usually tell us whether we are dealing with a benign tumor or a malignant tumor. Chu I have heard this expressed by some patients that they get extremely claustrophobic in tight quarters, and as I understand it, with MRI sometimes it's pretty tight quarters. What would you do in a situation where you have a patient who gets very fidgety and anxious at even the thought of undergoing an MRI? Lacy That's an important practical issue for the patients. MRI scans are absolutely critical to the management of brain tumors, so we really want to get an MRI instead of a CAT scan, which is easier for patients. There are open MRI scanners, but they are not quite as good in terms of the information that we get. We try to get patients through it; sometimes they do require a sedative to help with the procedure. Foss Is there any role for PET scanning in the diagnosis or management of brain tumors? Lacy Yes, PET scanning is one of the emerging diagnostic tools that we are using to help us define the biology of the tumor and help us determine if the tumor has recurred. A PET scan is a metabolic scan, it shows how metabolically active tissues in the brain are and we know that malignant tumors are very metabolically active; they are quite hot on PET. Benign tumors tend to be much less metabolically active, and in fact, cold. It's still somewhat of a research tool, and we are still learning how best to use and apply PET scanning in evaluating and managing brain tumors. Chu Jill, at Yale Cancer Center you are part of a team that works very closely together when evaluating patients with brain tumors. Can you tell us a little bit more about that? Lacy As I mentioned earlier, the management and treatment of brain tumors is very much interdisciplinary. It involves a neurosurgeon to get the biopsy or remove the tumor, a radiation oncologist to utilize radiation therapy as a treatment modality, an oncologist, either a medical oncologist or neurooncologist, who oversees administration of medications and chemotherapy, and a neurologist to manage seizures and other neurologic problems. Behind the scenes there is a neuroradiologist who is critical in interpreting the MRI scans, and the neuropathologist who we absolutely rely on for the diagnosis. It is a team and because of the complexity of treating brain tumors, and the number of specialists involved, there is benefit in being treated by a team of doctors that work very closely together. 15:19 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Apr-26-09.mp3 Foss Thank you very much Jill. We would like to get into

more detail about the types of treatment for brain cancer after our break. You are listening to Yale Cancer Center Answers, and we are here discussing the treatment of brain tumors with Dr. Jill Lacy. Foss Welcome back to Yale Cancer Center Answers. This is Dr. Francine Foss and I am joined by my co-host Dr. Ed Chu and Dr. Jill Lacy, a medical oncologist at Yale Cancer Center. Jill, in the first part of our discussion we talked extensively about the diagnosis of primary brain cancers, but sometimes when you think a patient has a primary brain tumor, you find out after biopsying that it is a different cancer, a cancer that spread from another part of the body. How often does that happen? Lacy As we had discussed earlier metastatic brain tumors are actually far more common than primary brain tumors. In most cases, patients with metastatic brain tumors already have a diagnosis of cancer outside of the brain, breast cancer or lung cancer, and so when they develop symptoms and have a scan and we see spots in the brain that are consistent with metastasis, we usually are fairly comfortable that that's the diagnosis and we don't have to get a biopsy. In some cases, however, patients with metastatic brain tumors will present for the first time, without a diagnosis of cancer, with neurologic symptoms and we will have a scan. There may be a lesion there and in some cases it may be difficult to distinguish a metastatic tumor from a primary brain tumor. In that case, of course, one must get a biopsy to make the diagnosis. Foss In terms of thinking about the primary therapy, we talked about surgery as playing a major role, can you tell us a little bit about the types of surgery that are done and if there are any alternatives to surgery? Lacy Conventional surgery to remove a brain tumor involves a craniotomy, which means that the surgeon will remove a small piece of the skull, expose the brain and the tumor, and carefully dissect the tumor away from normal brain and basically cut it out, if you will. Now, as I had mentioned earlier, there are some situations where the tumor cannot be removed surgically because it's either too deep within the brain and inaccessible, or it's located in a very critical area of the brain such as the speech center, and if one were to remove it, it would leave the patient with significant neurologic impairment. An alternative to surgery is something called radiosurgery, commonly referred to as Gamma Knife or CyberKnife. So what is radiosurgery? Radiosurgery is actually not surgery at all. It's a very specialized type of radiation where the radiosurgery device, say the Gamma Knife, delivers a very high dose of very focused radiation to a small area of the brain to the small tumor. The benefit of this is that you can deliver a high dose that's very focused without a lot of a scatter of radiation to normal brain tissue. Radiosurgery can ablate a tumor in basically the same way that removing the tumor surgically can accomplish; which is why it's often referred to as radiosurgery. It's quite a sophisticated technical procedure. It's usually done in one sitting with one treatment. It requires very sophisticated computer assisted technology to localize the tumor very precisely and usually involves putting on what is called a head frame or halo that is pinned to the scalp. Radiosurgery does involve an experienced team of physicians, once again a neurosurgeon, radiation oncologist, and radiation

physicists, and it's important that this procedure be done in the context of a radiosurgery team. Just as an aside, I would mention that we have a very robust and busy Gamma Knife Center here at Yale. It's one of the ten busiest Gamma Knife Centers in North America and is staffed by a very terrific team of physicians. Chu Say once surgery of the primary tumor is performed, is there any role for any type of follow-up therapy afterwards; such as either chemotherapy or perhaps radiation therapy? Lacy Yes. We talked about the important role of surgery, and in the case of benign tumors, surgery is often curative and there is no need for any additional treatments. However, with malignant tumors surgery is important. It relieves mass effect and symptoms and debulks the brain, but in most cases malignant brain tumors will grow back, and they actually will grow back quite quickly. So there is a need for what we call adjuvant therapies after surgery, and I think the treatment of the most malignant brain tumor, glioblastoma, illustrates how we use those adjuvant therapies. For glioblastoma we like to remove the tumor if we can, ideally, in its entirety, which is called a complete or gross total resection. We know that patients who are able to undergo a complete resection actually do better and have a better prognosis. But 21:57 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Apr-26-09.mp3 even in patients where all of the tumor that we can see is removed, glioblastoma always recurs and it recurs quickly. We have learned that administering radiation treatments after surgery significantly improves the outcome for these patients. So, if you do not do radiation, the tumor usually is back within three months, with radiation treatments often it's a year or more before the tumor recurs. Radiation treatments for malignant gliomas, including glioblastoma, use conventional radiation. Its small doses fractionated over usually five weeks, so the patient will come in every day, Monday through Friday, for radiation treatment. The radiation oncologist will treat the area of the original tumor, plus some surrounding brain, to try to kill any cells that have infiltrated into adjacent normal brain. Where does chemotherapy fit into all of this? This has been a recent advance in the treatment of glioblastomas. We learned a few years ago that administering chemotherapy, along with the radiation and after the radiation, significantly improves the outcomes for patients. The chemotherapy drug that we use is a drug called temozolomide, or Temodar. This was specifically developed to treat brain tumors. It's actually taken as a pill, and it has very few side effects. It's taken once a day throughout the radiation and then once radiation is finished, patients will continue on Temodar for at least six months to usually a year. What does Temodar accomplish? It's actually quite striking. The main benefit of Temodar is that it significantly increases the percentage of patients that are alive at late time points. So, for example, at two years 25% of the patients who get Temodar will be alive, compared to 10% of those who do not get Temodar. At five years its even more striking; 10% of patients who get Temodar are still alive whereas only 2% or less, who do not get Temodar, are surviving at five years. Temodar has had a very positive significant impact on the natural history of glioblastoma, and frankly, has been the biggest breakthrough in the treatment of this deadly disease over

the last several decades. Chu I am just curious, say for instance, in patients who might not be able to undergo surgery, but who receive radiosurgery, the Gamma Knife, CyberKnife procedure, is there any role for follow-up, either chemotherapy or whole brain radiation therapy after that radiosurgery has been done? Lacy It depends a little on the specifics and the type of brain tumor that we are dealing with. Radiosurgery is most commonly used to treat brain metastasis and benign tumors. We use conventional regional radiation to treat malignant tumors. Invariably there will be follow-up after radiosurgery, and serial MRI scans to assess the response to ensure that there is not a recurrence. Foss You talked about 25% of patients doing well a couple of years later. I am wondering, do most of those other patients relapse with their brain tumors, and if they do, what kinds of therapies do you use at that point? 25:19 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Apr-26-09.mp3 Lacy Malignant glioma is the most common brain tumor. In most cases it will at some point recur and when they recur, up to this point, we have not had highly effective therapies and rarely are recurrent gliomas ever cured. It's a very challenging area for us and certainly there is a real compelling need for new and better therapies to either prevent recurrence or to effectively treat recurrence when it happens. What has been exciting is that there have been some advances in the field that are related to the use of so called "targeted therapies" to treat brain tumors, so these are drugs that are developed specifically to target cancers, and in the treatment of brain tumors, many of these drugs look quite promising. One example is Avastin or bevacizumab. This is a targeted therapy that works by preventing blood vessel formation and it affects the blood supply to tumors. You may have heard about this drug in the media, it's got a lot of attention because it's quite costly. It's already approved by the FDA for use in breast cancer, lung cancer, and colon cancer, where it's used in combination with chemotherapy. In treating malignant brain tumors, Avastin, as it turns out, is very active, even in the absence of combining it with chemotherapy. It can dramatically reduce the swelling around the tumor, the mass effects of the tumors, the symptoms from the tumor, and in some cases shrink the tumor. Avastin, as it turns out, right now is probably the most effective treatment that we have for recurrent malignant gliomas. It's not yet FDA approved, but hopefully that will be coming soon. Chu Do you use that, as you say, as a single agent where it has activity, or do you typically combine it with standard chemotherapy? Lacy It can be used either way. It does have activity alone in brain tumors, which is in contrast to its use in say colon cancer, breast cancer, and lung cancer. Foss Are there other options for patients with brain tumors? Are there other new drugs that are being developed? Lacy Yes definitely. There are a number of very exciting and promising drugs in development, in clinical trials. Many of these are the so called targeted therapies as I just alluded to. In addition to Avastin there are small molecule inhibitors of angiogenesis, these are often taken as pills and are being developed and are showing considerable promise in the treatment of brain tumors. Chu Is there any research going on at Yale Cancer Center with respect to developing new approaches to

treat this disease?Lacy Yes definitely, we have a very active clinical research program at Yale, largely focused on the treatment of glioblastoma, the most malignant form of glioma. So for example, we have28:19 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Apr-26-09.mp3 a very interesting vaccine trial. In this trial, patients with glioblastoma will get standard of care radiation, Temodar, and in addition will get monthly injections of a vaccine. The idea here is to boost an immune response to the tumor and use the immune system to hopefully prevent the tumor from coming back. The preliminary data with this vaccine is really quite exciting.Chu It's amazing how time flies. Jill, we would love to have you back and hear more about this vaccine trial. You have been listening to Yale Cancer Center Answers. I would like to thank our guest Dr. Jill Lacy for joining us this evening. Until next time, I am Ed Chu from Yale Cancer Center wishing you a safe and healthy week.If you have questions or would like to share your comments, go to yalecancercenter.org where you can also subscribe to our podcast and find written transcripts of past program. I am Bruce Barber and you are listening to the WNPR Health Forum from Connecticut Public Radio.