

Yale CANCER CENTER answers

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Hosts

Edward Chu MD

Chief of Medical Oncology

Kenneth Miller MD

Director of Supportive Care

New Options to Treat Brain Tumors

Guest Expert: **Joachim Baehring, MD**

Associate Professor of Neuro-Oncology
Director, Yale Cancer Center Brain Tumor Program



Yale Cancer Center Answers
is a weekly broadcast on
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Sunday Evenings at 6:00 PM

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Welcome to Yale Cancer Center Answers with Dr. Ed Chu and Dr. Ken Miller. I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center. Dr. Miller is a medical oncologist specializing in supportive care and is the author of Choices in Breast Cancer Treatment. If you would like to join the discussion, you can contact the doctors directly at canceranswers@yale.edu or 1-888-234-4YCC. This evening, Dr. Ken Miller sits down for a conversation about the treatment of brain tumors with Dr. Joachim Baehring. Dr. Baehring is an Associate Professor of Neurooncology at Yale and he is Director of the Yale Cancer Center Brain Tumor Program.

- Miller Let's start by talking about some basic information. When people talk about a brain tumor, what are they referring to?
- Baehring The two major categories of brain tumors are those that primarily affect the brain, meaning that they start in the brain, and metastatic brain tumors. Patients who have cancer in the lung and the breast can develop metastases, seeding of the tumor to the brain. Those are the two major categories.
- Miller What is more common?
- Baehring More common are the metastatic tumors, probably by about five fold, maybe even 10 fold.
- Miller So there are a group of people who unfortunately develop a cancer that starts in the brain itself?
- Baehring Yes.
- Miller In broad categories, what are the different types of cancer that arise in the brain?
- Baehring There is a large variety of primary brain tumors. The largest group of brain tumors is called gliomas. That term is derived from a normal type of cell that exists in the brain and that cell type is called the glial cell. Tumors that resemble those cells, and likely are derived from those cells, are called gliomas, and amongst those tumors there are benign variants and malignant variants, or cancerous variants. The most common tumor, unfortunately, is a malignant one and it is called glioblastoma.
- Miller So there is a glioma, which is a low-grade one, and a glioblastoma, which you were just referring to. What are the differences, do they look alike under the microscope, or do they behave differently?

- Baehring Again, there is a large group and some of the low-grade tumors are quite different from the high-grade ones; those tumors may even be curable by taking them out. However, there is an overlap between the “low-grade” ones and the malignant ones. Those tumor groups are called astrocytoma, or oligodendrogloma, and they can be diagnosed at a stage where they look very benign, but over the years they can transform into a higher grade tumor and then behave more aggressively. There is an overlap between the two groups and one can transform into the other, unfortunately.
- Miller Let me ask a question that I think a lot of people are wondering about, what goes wrong with a normal cell to make it become malignant, and what are the risk factors?
- Baehring There are many very well-established risk factors for various types of systemic cancer. However, for brain cancer, we have not really identified major risk factors. The only one where there is a clear correlation between exposure and later development of brain cancer is with radiation. Patients who in their childhood had a tumor affecting the brain, let's say patients with leukemia who require radiation to the brain because the leukemia had spread there, later in life they have a risk of developing a brain tumor in the area that was radiated. Other risk factors really have not been consistently linked to brain cancer. Very small subsets of patients with brain cancer have a genetic predisposition. I would say at a center like ours, we may see one or two cases a year amongst over 100 newly diagnosed cancers. So, that is quite rare.
- Miller A million dollar question, but a common question people ask, do cellphones cause brain cancer?
- Baehring I don't think at this point there is any evidence that they do. There are many studies across the world, most of which seem to suggest there is no correlation between the use of cellphones and the risk of developing brain cancer. However, as with many other exposure risks, many times they are ruled on decades after the exposure was initiated, so there may be a slight increase in risk, but again, there is absolutely no evidence, neither from animal experiments nor from studies in humans, that cellphone use increases the risk of brain cancer. Cellphones have been around for a long time, so I think the likelihood that we will ever establish a link is quite low.
- Miller Which absolutely is reassuring because you see almost everybody with cellphones in their hands. Typically, what are the symptoms someone would have? You see a large number of new patients here, what do they tell you?

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- Baehring The two most common symptoms that patients presents with, that are later found to have a brain tumor, are headaches and seizures. A headache is obviously a very common symptom, and probably one of the most common symptoms that people seek medical advice for. One does not have to be concerned about developing a brain tumor with every headache, obviously. Headaches are stress related, migraines are another stress related, very common, form of headaches, and there are various other types of headaches that are not caused by brain tumors. There are a couple of features that should alert somebody who has a chronic headache that they should have it checked out. The typical brain tumor headache is worst upon awakening in the morning. Patients even wake up in the middle of the night, and they may feel nauseated. Then once patients get up and walk around it gets better, and gets better during the day; at the end of the day they may not even have it. A headache that is chronic and gets worse week after week, month after month, that becomes more frequent, in general that is the type of headache that you don't just want to treat with over-the-counter medication, but see a doctor for.
- Miller That is important advice, but just to reassure people, as you were saying, headaches are very common, and thankfully, most of the time are not related to a cancer but to a benign cause. How do you detect a cancer in the brain?
- Baehring Once you have taken a history from the patient, examined the patient, and found a concern for a tumor, the next step is usually obtaining an imaging study of the brain. Nowadays, at least here in the US, the most commonly used diagnostic test is an MRI scan of the brain with contrast dye. It is the most sensitive and specific noninvasive test that we have, and that usually can rule out the presence or absence of a brain tumor.
- Miller There has been a lot of talk about newer ways to image the brain and understand how the area where a tumor is relates to the functional parts of the brain that control speech and vision. If you are contemplating having a patient have surgery, and you want to relate it to what they may lose in terms of function, how do you do that using imaging studies?
- Baehring There are a couple of new very interesting techniques, and the ones that I use nowadays are all MRI based, so for the patient there is not much of a difference having a regular MRI scan or one of these specialized MRI scans. If surgery is needed in an area that carries very important function like speech or strength on one side of the body, an MRI scan called a functional MRI is obtained where the patient is asked, while lying in the MRI scanner, to perform a certain task, either read from a text or listen to a verbal command or simply squeeze a soft ball in one hand, and the MRI

can actually pick up differences of blood perfusion on the surface of the brain and areas that are activated generally require an increased oxygen demand and blood supply. That relative difference is picked up by the scan and then a computer program can generate a color-coded map where the activated area is highlighted in relationship to the tumor, and that provides very important information to the neurosurgeon in determining whether this tumor can be safely removed, or if removal would likely result in a neurologic deficit, then only a biopsy be performed.

Miller This sounds fascinating.

Baehring It is.

Miller I have heard for a long period of time, of having a neurologist or a specially trained person in the OR doing an EEG or doing other studies. Can you tell us a little bit about that, the intraoperative part of things?

Baehring Yeah, tests like that are still indispensable. The preoperative imaging capabilities have dramatically improved. However, in the very end when it comes down to making a decision as to whether a piece of the tumor can be safely resected or not, the neurosurgeon still does some intraoperative testing and there are various options such as simply stimulating the surface of the brain with an electrode, and if a tumor is located very close to the language area, sometimes patients are only lightly sedated for the surgery, and then in the operating room, the medication is briefly withdrawn. The patient is asked to read something before and after stimulation, and if there is a change in language function after stimulation, the surgeon knows that they cannot remove that part of the brain. Also, stimulation in a patient who is sedated off the strength control area, the brain results in contraction of muscles on the opposite side of the body. So, if a surgeon elicits that kind of response with stimulation, he knows this is an area where they cannot go.

Miller Fortunately it sounds like that aside from the physical exam and your expertise, you also have a lot of tools available to you to help make those decisions.

Baehring Yeah, the technology has evolved quite dramatically, and while there are a lot of tumors still that we cannot cure, the outcome from surgery has improved simply based on the fact that we can determine the relation of the tumor to the normal brain much better.

Miller How is a biopsy done?

- Baehring A biopsy can be done one of two ways, either the skull is opened like for regular surgery and then a small piece of the tumor is taken out, or a way that is less invasive, is what you call a stereotactic biopsy. A patient is taken to the operating room, a small bur hole is drilled into the skull, and then a fine needle is inserted into the area of interest into the tumor and then a very small tissue cylinder, it is only about a millimeter thick and about a third of an inch long, is retrieved and then the pathologist looks at the tissue.
- Miller Are there ever times where you are unsuccessful in getting a biopsy and you have to just decide to treat someone?
- Baehring Sure, that does happen. If a brain tumor is in a very critical area of brain function, if it is very deep in the brain, or if it is in the lower part of the brain in what is called the brainstem, there are a lot of vital functions like breathing located there. Sometimes either a biopsy cannot be performed because it would be unsafe for the patient, or only a very small piece can be retrieved, on which a diagnosis is not possible. That is rare, but it does happen. If the patient's symptoms progress, we are bound to treat based on imaging appearance and other test results, we simply have to treat for the most likely diagnosis.
- Miller Those must be very difficult situations. Before taking a break, let me ask you, what is the primary form of treatment for people with a cancer that arises in the brain?
- Baehring For most cancers of the brain, for most malignant brain tumors, the treatment approach requires several specialties. Typically, the surgeon is the first involved either for a biopsy or removal of the tumor. Secondly, the radiation oncologist provides radiation to whatever of the tumor is left and possibly also to some degree of normal-appearing brain around the tumor. Thirdly, chemotherapy is a tool for many different types of brain tumors. There are variations. There are particular tumors that can be cured by surgery. There are other tumors that are very sensitive to radiation and other tumors that go away with chemotherapy alone, but as a general rule for the most common tumors like glioblastoma, all three treatment modalities are required.
- Miller You are listening to Yale Cancer Center Answers. We are here discussing the latest in treatment options for brain tumors with Dr. Joachim Baehring who is an expert in the treatment of these types of tumors at Yale Cancer Center. We are going to take a break for a medical minute and will be right back with you.

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Medical Minute

It is estimated that over two million men in the US are currently living with prostate cancer. One in six American men will develop prostate cancer in the course of their lifetime. Major advances in the detection and treatment of prostate cancer have dramatically decreased the number of men who die from this disease. Screening for prostate cancer can be performed quickly and easily in a physician's office using two simple tests, a physical exam and a blood test. Clinical trials are currently underway at Federally Designated Comprehensive Cancer Centers like the one at Yale to test innovative new treatments for prostate cancer. The patients enrolled in these trials are given access to experimental medicines not yet approved by the Food and Drug Administration. This has been a medical minute and you will find more information at www.yalecancercenter.org. You are listening to the WNPR Health Forum from Connecticut Public Radio.

- Miller Welcome back to Yale Cancer Center Answers. This is Dr. Ken Miller and I am joined today by Dr. Joachim Baehring who is an Associate Professor at Yale Cancer Center and an expert on the treatment of malignant tumors of the brain. Joachim, we started talking about treatment of cancers that arise in the glial cells, glioblastoma and tumors like that. I also know that you are an expert in the treatment of patients with lymphoma of the brain. Can you tell us a little bit about that, I mean we typically think of lymphomas and the lymph nodes, how does it arise in the brain?
- Baehring Brain lymphoma is quite a rare tumor. There are only about 1000, maybe 1400, cases a year in the United States altogether. Just for comparison, for colon cancer and prostate cancer, there are over 200,000 cases a year in the US. So it is in order of magnitude less frequent. Lymphoma, you are right, typically affects lymph nodes, but also other organs of the body can be affected like the liver, spleen, heart, lungs or the brain. Of all lymphomas that arise in the United States, only 1 in 50 affects the brain alone, and it is a rather peculiar tumor in that it seems to affect only the brain. Only at the very last or late stage when the tumor relapses after initially successful treatment, does it leave the brain and spread into other parts of the body. There is a unique predilection for the brain with these tumor cells, and we believe that these tumors arise from cells that at some point during the patient's lifetime were primed to attack some intruder, bacterium or virus in the brain, and that is why they later seek out the brain again, but that is a hypothesis and has not been proven yet, but it seems to be true for other types of lymphoma.
- Miller If a patient has a central nervous system lymphoma, is the treatment in that case surgery, chemotherapy, or radiation?

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- Baehring Lymphoma happens to be exquisitely sensitive to chemotherapy, so it has a rather typical appearance on MRI. If we suspect a lymphoma, typically the surgical procedure is limited to a stereotactic biopsy, meaning biopsy through a small bur hole. If the diagnosis is confirmed, then chemotherapy is administered. There are different types of chemotherapy regimens, all of them include a drug called methotrexate that is given by vein every two to four weeks over the course of 6 to 12 months. There is about a 60% to 70% chance that the tumor will go away with that treatment.
- Miller Which is excellent and probably a lot better than it was years ago.
- Baehring The treatment paradigms have changed. In the old days these tumors too were treated with surgery and then radiation and the patients either had severe side effects from those treatments down the line, anywhere 6 months or 12 months down the line, or the tumors relapsed fairly quickly. About 15 years ago there was a change in the treatment paradigm and that has improved the outcome of patients with these tumors dramatically.
- Miller I want to switch to a different topic. We have talked some about surgery, we have talked about chemotherapy, but you and the team you work with are also experts in the use of gamma knife radiation, what is that?
- Baehring A gamma knife is a device that provides a radiation boost to a defined area within the brain. The core feature of a gamma knife is actually a large shielding device and the radiation source surrounds this shielding device. There are over 100 bur holes in that shielding device and they can be focused on an area within the brain that is abnormal, may that be a tumor. There are other indications for this procedure as well. The advantage is, if the x-ray beam comes from different directions and all the beams meet in one target, the exposure of normal brain surrounding the problem is minimized, whereas the tumor exposure is maximized. That is in contrast to standard radiation where the x-ray beam may be from three or four directions and that exposes normal brain much more than gamma knife does. Gamma knife is not for everybody and tumors that are not very well circumscribed, and unfortunately most of the primary brain tumors are not, are not good targets for gamma knife simply because the treatment then only focuses on the very core of the tumor, but it does not address less obvious tumor surrounding this lesion.
- Miller Let's stroll down a little bit further on this, your description of the gamma knife has been very helpful to me. For patients with a glioblastoma, which you were saying is the most common type of brain tumor, who has surgery, would you want to give them external radiation, or the typical

radiation, or would you want to use gamma knife?

- Baehring The standard treatment protocol for a glioblastoma consists of a standard radiation protocol, meaning “involved field radiation” where not only the tumor and whatever is left after surgery is exposed to radiation, but also a safety margin of about two thirds of an inch to one inch that surrounds the tumor, and that simply addresses the nature of the tumor. The tumor is not circumscribed, it is not surrounded by a capsule, it is not sharply separate from the brain, but it has very fuzzy edges. There are tumor cells that infiltrate the brain surrounding the tumor that is visible on MRI scan. A gamma knife is used for patients with glioblastoma; however; there are very selective indications for it. If a patient after surgery has a very small residual, or after initially successful treatment has a very small recurrence, that may be an inappropriate target for a gamma knife, but gamma knife has been studied formally for glioblastoma in addition to a standard radiation, and unfortunately, that did not lead to a survival advantage.
- Miller I think people sometimes have the impression that hi-tech is better. You hear about gamma knife or cyber knife, and I think this assumption is that they are better, but in this case it is not.
- Baehring That's right. There is a select small group of patients that would benefit from additional radiation boosts, but one really has to select these very carefully.
- Miller What does adjuvant therapy mean? And how is it applied to people with brain tumors?
- Baehring Adjuvant really means additional therapy after surgery, that's what we mean with adjuvant. So, in a way, radiation treatment is an adjuvant treatment and so is chemotherapy. For patients with primary brain tumors, as I mentioned, most patients do need both the primary treatment, which is surgical removal of as much of the tumor as we can, and adjuvant treatment such as radiation and chemotherapy.
- Miller What type of chemotherapy is used for patients like these?
- Baehring For the most common primary brain tumor, the standard of care now includes a drug that is called temozolomide. It is a drug that is given by mouth and it alters the molecule, the DNA molecule, within the cancer cell that carries the genetic information, and by doing so, it interferes with the ability of the cancer cell to divide, which is ultimately the basis for tumor growth.

- Miller What are some options for patients with brain tumors, and in particular, are there any clinical trials that are available?
- Baehring There is a large number of clinical trials available. Over the last 10 years we have seen numerous new drugs enter the field being tested in clinical trials. There are a couple of drugs that are of particular interest to patients with primary brain tumors. One I want to highlight is a group of drugs that targets the tumor's ability to grow new blood vessels when tissue grows at a high rate like in cancer. Tumor cells and tumor growth is dependent on oxygen supply, a nutrient supply, that requires growth of blood vessels. So, there are drugs that can specifically target the tumor's ability to do that. There are different mechanisms. Some of these drugs are given by vein, others by mouth. For some drugs we already have some clinical trial data that is quite encouraging. There is a drug called bevacizumab that has gone through the first phases of clinical trial. There are other drugs that are a little earlier in the development. However, we do not have definitive trial results yet that would tell us why all of these drugs need to be included in the standard of care, but we are probably getting close to at least identifying one or two more drugs that may be added to what we have been doing so far; radiation and standard chemotherapy.
- Miller It makes me think back to the situation with lung cancer and colon cancer where bevacizumab, or Avastin, seemed to work synergistically together with chemotherapy. Might that apply to treatment of people with brain tumors?
- Baehring There is certainly evidence from experiments that there may be a synergism between bevacizumab, or other drugs that attack the ability of the tumor to grow blood vessels, and standard forms of chemotherapy. There is a drug called irinotecan that in experiments, at least, has been shown to have a greater effect on tumor cells if it is given in addition to bevacizumab.
- Miller And some of the research that is going on at Yale is very exciting, for example the use of viruses to attack the brain, and new methods of delivering therapy, can you tell us some about those?
- Baehring There are several groups at Yale with an interest in brain tumors, and the two different topics you mentioned are probably the hottest that are currently ongoing. One group in our department, led by Anthony van den Pol and Guido Wallman, is trying to identify viruses that not only have the ability to specifically infect tumor cells, but also then kill them. They have been successful and have shown in animal experiments that tumors that

are growing in the brain can be successfully treated with this. However, there is still a long way to now transfer this knowledge into a clinical trial where patients are actually treated. There are examples of different viruses that have already been used in clinical trials in humans. This would be a refined origin of those viruses and I am hopeful that over the course of a few years we will get there and can use some of these new tools. There is another group at Yale that is led by Dr. Saltzman, the director of the Department of Biomedical Engineering, and he is developing “micro vehicles” with which we can administer drugs, or other treatments, directly to the brain. Those vehicles are called nanoparticles and they are microscopic particles that can be coated with certain molecules that renders them specific for brain cancer cells. They can be loaded with different agents that can attack brain cancer. This is quite an exciting field of research and I think that is a little closer to clinical use in the viral treatment.

Miller Sitting here with you, I have to share with the listening audience, I can see your eyes light up when you are talking about these; it's exciting isn't it?

Baehring You know, these are exciting times.

Miller That's terrific. How can a patient access help from the brain tumor center?

Baehring We can both evaluate patients, as in a primary consultation, and then treat them, or we also provide second opinions. If a patient is interested in simply coming in or sending us material, we will review the case in our multidisciplinary tumor board and then provide an opinion as to how we would approach the case. But for anything general, we have a clinic coordinator, Elizabeth D'Andrea. She can be reached at Yale at 203-737-1671. She is the first contact person through which patients enter the system, and she makes the decision if that patient should be seen first by a surgeon, a radiation doctor, by myself, or one of our other medical oncologists.

Miller Terrific, you have been listening to Yale Cancer Center Answers. I want to thank our guest, Dr. Joachim Baehring, for what has been a really interesting session for me, and I hope for all of you as well. Joachim, thank you.

Baehring Thank you for having me.

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Miller Until next week, I am Dr. Ken Miller from the Yale Cancer Center wishing you a safe and healthy week.

If you have questions for the doctors or would like to share your comments, go to www.yalecancercenter.org where you can also subscribe to our podcast and find written transcripts to past programs. Next week, you will meet Dr. Melinda Irwin who joins Dr. Ken Miller to talk about exercise and cancer prevention. I am Bruce Barber, and you are listening to the WNPR Health Forum from Connecticut Public Radio.