Yale CANCER CENTER *answers*

WNPR Connecticut Public Radio

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Treating and Living with a Brain Tumor

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Welcome to Yale Cancer Center Answers with Drs. Ed Chu and Francine Foss, I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center and Dr. Foss is a Professor of Medical Oncology and Dermatology specializing in the treatment of lymphomas. If you would like to join the conversation, you can contact the doctors directly. The address is canceranswers@yale.edu and the phone number is 1888-234-4YCC. This evening, Ed welcomes Dr. Joachim Baehring. Dr Baehring is Director of the Yale Cancer Center Brain Tumor Program and he is an Associate Professor of Neuro-oncology. Here is Ed Chu.

Chu Why don't we start off by defining what brain cancer is?

Baehring Essentially there are 2 types of brain cancer. Primary brain cancers are cancers that arise directly in the brain, and then there are metastatic brain cancers, which means cancer lesions have arisen in the brain as metastasis from a systemic tumor elsewhere in the body.

Chu For today's discussion we are going to be focusing on that first type of brain cancer called primary brain cancer. But let's follow up with, what are the types of other cancers that commonly spread to the brain?

Baehring You mean systemic cancers?

Chu Yeah, the metastatic cancer type.

Baehring The most common cancers that spread to the brain are breast cancer and lung cancer, and at the same time those are the most common cancers in general. Other cancer that is overall less common, but may have a high risk of seeding to the brain, for example, is malignant melanoma.

Chu So getting back to primary brain cancer, how common is it? About how many patients each year are given this diagnosis of primary brain cancer? Then I guess within primary brain cancer, there are a number of different types of subcategories.

Baehring Right, there are a large number of subcategories. Overall, there are about 45,000 cases of primary brain tumors in the United States; that does not equal brain cancer. That includes benign tumors, cancerous tumors, and malignant tumors, if you will. The most common primary brain cancer is called glioblastoma multiforme, and there are about 8,000 to 10,000 cases in the US per year, and that compares to over 100,000 cases of colon cancer, and over 200,000 cases of breast cancer and prostate cancer, so you can tell brain cancer is rare, fortunately. There are numerous subtypes, I mentioned glioblastoma which is the most common one. Another very common brain tumor, which is benign, is called meningioma. That is a tumor that arises from the covering of the brain and is generally curable by taking it out.

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Chu In what age group do we typically see these brain cancers?

Baehring As with other cancers, brain cancer is usually a disease of older age, so the older we get the higher the risk is of developing brain cancer, and that applies to the most common primary brain cancers. There are exceptions, there are cancers that arise particularly at young age in childhood. There is a tumor of the balance center of the brain called medulloblastoma which is much more common in children than it is in adults, but as a general rule, the older we are the higher the risk is of developing brain cancer.

Chu What do we know about the main risk factors for developing brain cancer?

Baehring There are very few that actually have been proven to lead ultimately to brain cancer, one known risk factor is exposure to radiation, therapeutic doses of radiation. For example, if someone suffered from childhood leukemia and underwent radiation treatment to the whole brain, either for treating leukemia in the brain or preventing leukemia from seeding to the brain, those patients are at higher risk later in life to develop a number of brain tumors including malignant brain cancer. That is really the most solid risk factor that we know of. There are some other environmental risk factors that are discussed and have been investigated numerous times, but the one of most concern is exposure to cell phones. I think we still do not have very solid data as to whether the risk for brain cancer has increased in cell phone users, and I do not think we have a good sense as to how much cell phone use would be unhealthy. I think as a general rule it is reasonable to limit the exposure to cell phone or other phones of electromagnetic waves to a minimum, and use devices that limit the exposure, but again the link really has not been established yet.

Chu It is interesting because I guess there have been earlier studies to show that in fact, there was an increased risk, but I guess that was using the old analog cell phones, and it was unclear that the people were using cell phones quite as frequently as they are now. It is really pretty amazing at how young in age people are starting to use cell phones, and they seem to be on it for a long period of time.

Baehring That's true, yeah, some people use cell phones as a main device to make phone calls rather than to just make a quick emergency phone call on the road, but again, there is no study that would tell us how much cell phone use is too much, and whether there is an increased risk to begin with.

Chu And what about dental x-rays, because I know people have asked me if they have too many dental x-rays could that put them at increased risk, is there are any truth to that at all?

Baehring There is no data that would link plain x-rays for dental procedures to brain cancer. I think as with everything, we should limit medical procedures including these x-rays to the absolute minimum. I

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think the current standards in terms of frequency of these x-rays are reasonable and at that frequency there is no clear link to brain cancer.

Chu Is there any genetic component, any genetic basis for brain cancers, so if someone in the family has had brain cancer, does that increase the likelihood that a sibling or a child could develop brain cancer?

Baehring There are certainly genetic risk factors; however, they are rare. There are a couple of conditions. The most common one is called neurofibromatosis, and those patients have a certain gene defect that renders them susceptible to developing all kinds of tumors affecting both the peripheral and central nervous system. In the overall scheme though, the number of patients who develop brain tumors based on one of those predisposition syndromes is probably less than 3%. And then again, cancer is common, so if a patient who has brain cancer has several family members with a cancer history, that may not be alarming to begin with. If patients have the same kind of tumor within one family, only certain types of tumors, and they develop these tumors at an unusually young age, then one should pursue investigation of whether predisposition exists within that family.

Chu In terms of symptoms that an individual might experience, what should one look out for?

Baehring Brain tumor symptoms are rather nonspecific. A lot of disease processes affecting the brain can present with symptoms very similar to how a brain tumor would present. The two most common initial presentations are headaches and seizures, so especially somebody who develops seizures late in life, in the range of about 40 years of age, lets say, that is somewhat concerning and generally it suggests that there is a structural problem within the brain and many a times that is a tumor. Headaches are obviously amongst the most common symptoms that we go seek medical advice for and the vast majority of headache causes are benign ones. In terms of headaches, if a patient wakes up in the morning with a headache and feels nausea, and then as the day goes on the headache improves, but then over time week-after-week, month-after-month, those headaches get worse, that is the type of headache that is more concerning as opposed to the tension type headache that we all get, that gets worse at the end of the day and then the next morning after a good night sleep or massage it has gone. That really does not raise any concerns.

Chu What period of time would you say should one get concerned; if the headache persists for more than a week or two and does not seem to get better?

Baehring Yeah, it also depends a little bit on the intensity, if it is a mild, dull pain, and the patient had a work out or did some strenuous work, some heavy lifting, then that kind of activity can set off a tension type headache, and that can linger on for longer, but especially if there is progression, no clear

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explanation for the headache, after a period of maybe a week or two, one should at least ask the family doctor for a checkup.

Chu So the next person that should be seen is the general internist or the family physician?

Baehring I think that would be the first doctor to see, and the family doctor can first of all take a good history and do a thorough examination and if there are certain concerning features then maybe that doctor would order the first imaging study, or then refer the patient for neurologic evaluation, or if there is particular concern about a tumor then to a neuro-oncologist.

Chu So, you would recommend from the family physician then seeking attention directly to a neuro-oncologist specialist like yourself as opposed to say a more general neurologist?

Baehring It depends a little bit on the symptoms. Frequently it works that way. If the patient has a headache that gets worse and worse and the family doctor already orders an imaging study and that shows a mass lesion, then patients are referred directly to us. If the symptoms are a little less clear, let's say the patient develops some strange sensory loss on one side of the body or something like that, then frequently the family physician refers those patients to a general neurologist to rule out neurologic conditions that are much more common than brain tumors.

Chu What would be the usual imaging studies, x-ray studies, that would be done to try to make a diagnosis of brain cancer?

Baehring The most sensitive and specific test for diagnosing a brain tumor would be an MRI (magnetic resonance imaging). A CAT scan serves the purpose of ruling out an acute event that would constitute an emergency such as stroke or a bleed within the brain, and sometimes it's used as a screening test to make sure that there is no major tumor within the brain. But if there is really any concern then an MRI should be obtained, and those scans are done with contrast dye, and brain cancer does light up on these studies and it is fairly easy to diagnose.

Chu So then say once something suspicious is seen on the MRI or CAT scan, what would be the next step?

Baehring If there is concern for a brain tumor then a definitive diagnosis requires that a piece of tissue is obtained from that lesion and that requires a neurosurgical consultation. If the tumor can be removed in its entirety, and it seems to be a tumor that would best be treated that way, then patients undergo full surgery and the tumor is removed to the largest possible extent without causing any injury. If the tumor is of a kind that responds favorably to chemotherapy, or if the tumor is located in the critical area of the brain where surgery would lead to a disability, then the surgical procedure

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may be limited to a small biopsy, and in that case, only a small burr-hole is drilled into the patient's head, and then a small sample is retrieved with essentially a needle.

Chu Can you tell us a little bit about how you evaluate patients?

Baehring Most patients come to me referred by another physician so they do come with imaging studies, and sometimes I am the one who does the initial workup, but the evaluation consists of a thorough history and physical examination and review of the imaging studies. If a surgical procedure has already been performed, we review the report first and then refer the entire case essentially to what we call of a tumor board, which is a multidisciplinary conference that takes place once a week during which we then review the actual pathology slides, those sections that are performed after the tumor tissue has been removed, and then these sections are looked at under the microscope to determine what type of brain tumor it is. The treatment plan is then generated by our multidisciplinary team, the neurosurgeons on that team, the medical oncologist, the neurologist, the radiation oncologist, pathologists, doctors specialized on the analysis of the tumor tissue, and radiologist specialists to interpret imaging studies.

Chu Great, and maybe on the other side of the break we can talk a little bit more about this multidisciplinary approach to treating patients with brain cancer. We are going to take a short break for medical minute. Please stay tuned to learn more information about the evaluation and treatment of brain tumors with our guest expert Dr. Joachim Baehring from Yale Cancer Center.

Medical *Minute* *There are over ten million cancer survivors in the US and the numbers keep growing. Completing cancer treatment is very exciting, but cancer and its treatment can be a life changing experience. After treatment, to return to normal activities and relationships can be difficult and cancer survivors may face other long term side effects including heart problems, osteoporosis, fertility issues, and an increased risk of second cancers. Resources for cancer survivors are available at federally designated comprehensive cancer centers such as Yale Cancer Center to keep cancer survivors well and focused on healthy living. 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.*

Chu Before the break we were talking about the multidisciplinary approach to treat patients with brain cancer, and you were telling us about how your multidisciplinary clinic and tumor board functions. For those who may have missed the first part of this interview, can you review all of the different oncology disciplines that are involved in this clinic and the tumor board conference?

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Baehring We have two platforms to provide multidisciplinary care. On one side, we have the multidisciplinary clinic where doctors of various subspecialties evaluate patients at the same time and at the same place, and then we have the tumor board, which is a multidisciplinary conference. In our multidisciplinary clinic, we have neurosurgeons, we have a medical oncologist, a neurologist, and a radiation oncologist, and new patients especially are evaluated at the same time. So, if we get a referral either for management or as a second opinion, we see these patients as a team. The tumor board then is a platform where we can discuss patients in more detail, where we can review the imaging study with one of our neuroradiologists who is a specialist on brain tumor imaging, with our neuropathologist, who is the doctor who analyses the tumor tissue, and then as a group we can come up with the treatment plan, and that may be a standard treatment plan with an established treatment regimen, or it may be a clinical trial.

Chu And again, maybe you can very briefly review the different types of treatments that can be offered to patients.

Baehring Most patients with brain cancer require this multidisciplinary approach. The first step is usually surgery, which may be simply to retrieve a small piece of tissue to make the diagnosis, or remove the entire tumor as a first step of treatment. Then the second step of treatment depends on the type of tumor that we encounter, for many tumors combined radiation and chemotherapy is required. For example, the most common tumor that we talked about in the first part of the interview, glioblastoma multiforme, requires both radiation and chemotherapy. The chemotherapy for that tumor comes in pill form and then treatment is administered over a six-week block followed by additional chemotherapy down the line. There are other tumors. There is a tumor called primary CNS, or central nervous system lymphoma, which is exquisitely sensitive to chemotherapy. So those patients usually only undergo a biopsy and then go directly on to chemotherapy, and there are tumors that are surgically curable such as meningioma. So these patients do not need the radiation doctor, or me. And then there are tumors that are very sensitive to radiation. For example, there is a tumor of the brain that is called germinoma. It is a germ cell tumor of the brain and that can be cured with radiation. So you can see there are algorithms in place for different types of brain tumors and there is a large number, and every single subdivision is relatively uncommon.

Chu Joachim, what is gamma knife? We hear that term used a lot. Is that a surgical procedure, and when would you consider using gamma knife as a treatment approach?

Baehring The name almost implies that it is a surgical procedure, but it is knifeless, although it is called gamma knife. This is a radio-surgical procedure. Radio-surgery entails the administration of a very focused beam of radiation to a defined area of interest within the brain. So, for example, if

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the patient has a tumor that is very deep in the brain that is not considered a surgically removable tumor, is not responsive to chemotherapy, or a tumor that is no larger than about 2/3 to 1 inch in diameter, that would be an ideal target for a gamma knife radio-surgery. This is a one-day procedure. Essentially, patients come into our gamma knife centre, a frame is attached to the patient's head which assures that patients are in a defined position within the device and then after very complicated and careful planning, the radiation boost is administered to that lesion and that really concludes the treatment, but there is no cutting involved.

Chu I have also heard the term CyberKnife used. Is that the same as gamma knife, or is that slightly different?

Baehring It is similar, but not the same. Gamma knife, as I mentioned, requires that a firm frame be attached to the patient's head to make sure that the x-ray beam is truly administered to the area that is supposed to be radiated. In the other techniques, like CyberKnife, there are numerous other techniques that follow the same principle. The targeting of the x-ray beam is based on plain x-rays. So, x-rays are taken off the anatomical area of interest from different angles and then through a computer algorithm that information is used to guide the x-ray exactly to the target that is supposed to be radiated. You call that image-guided sterotactic radio-surgery as opposed to the frame-based radio-surgery which is gamma knife. Technically, these are different techniques; however, both serve the purpose of eradicating a very focused problem. One big difference is that the image-guided radio-surgery can be used anywhere in the body as opposed to gamma knife which can only be used in the head.

Chu By having such a focused delivery of radiation therapy, that can help to reduce, minimize, the toxicity as well?

Baehring Absolutely, first of all, one can administer a higher dose to the cancer, meaning the cell killing will be more efficient. On the other side, the beam is so focused that the surrounding tissue is not exposed to this large dose. So, that is a major advantage of these radio-surgical procedures compared to standard radiation.

Chu Joachim, maybe you can just talk a little bit about the role of biological targeted therapy. We hear that term used a lot for the treatment of a wide range of other cancers, but as I understand it now, targeted therapy has also come to the treatment of brain cancer.

Baehring Yeah, that is an extremely exciting area of research, and as you mentioned, many of these treatment concepts have already found their place in standard treatment protocols, or clinical trials. "Targeted therapy" means that tumor cells are attacked through specific growth promoting, or growth inhibiting mechanisms. The old fashioned chemotherapeutic agents are un-targeted; they

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have different targets. Maybe some of the newer agents are specifically targeted to one specific molecule. For example, in brain cancer, growth of a brain cancer many times is driven by a receptor molecule on the surface of the cells. It is called EGFR, or epidermal growth factor receptor. Now, there are targeted therapies available that specifically render this receptor dysfunctional, and thus, decrease the flow of signal through this growth-promoting pathway. Now, that is not unique to brain cancer. These drugs were developed first for a lung cancer and other types of systemic cancer, but many of these treatment concepts do apply to brain cancer as well. There is another targeted form of treatment that does not attack the tumor itself; it attacks the tumor's ability to form new blood vessels. You call those antiangiogenic therapies and there are numerous mechanisms at various levels that one can use and that is one of the most exciting new treatment forms for cancer in general, and for brain cancer specifically.

Chu In fact Avastin, which is the main antibody that is used to treat colon cancer, lung cancer, and breast cancer, as I understand was recently approved to treat glioma.

Baehring Yeah, bevacizumab, the brand name is Avastin, targets a molecule called VEGF, vascular endothelial growth factor protein, that is required to form new blood vessels by the tumor and that was approved by the FDA in May of this year for relapse glioblastoma, meaning glioblastoma that has failed the first line of attack which is radiation and the chemotherapy with a drug called temozolomide.

Chu And how is this drug Avastin handled; are there many side effects associated with this?

Baehring It is actually tolerated fairly well. Avastin, and other drugs within that group, can increase the blood pressure and sometimes patients have to be started on a medication to lower the blood pressure. It can have an effect on the kidney, limiting the dose of the Avastin, and it can cause wound healing problems, but in general, it is fairly well tolerated across all age groups that we treat.

Chu Your group at Yale Cancer Center has been very interested in developing new approaches to treat brain cancer. Maybe you can tell us a little bit about what is going on in that area?

Baehring We have a number of investigators at Yale who are interested in developing new treatment strategies for brain cancer, and there is one group that is interested in using viruses, genetically-modified viruses, to specifically attack and kill brain tumor cells. That is a group led by a Tony van den Pol, from the department of the neurosurgery. We have a wonderful department led by Mark Saltzman, by our medical engineering, and his group is trying to develop particles, they call them nano-particles because they are micro particles, that can be administered directly into the brain and then slowly release a therapeutic agent, may that be a classical chemotherapy agent

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or one of the newly developed agents, and it is our hope that with these nano-particles we can deliver a higher concentration of compounds directly into the brain not exposing the rest of the body to the possible side effects from these drugs.

Chu So, these nano-particles would be administered by a neurosurgeon?

Baehring In all likelihood one could properly generate nano-particles that can be given through a vein; however, then one would have to worry about whether these particles can make it to the brain tumor and the systemic side effects, side effects to the whole body. One way to administer these drugs would be through direct infusion into the brain, so at the time the tumor is taken out, the neurosurgeon would insert micro-catheters into the normal brain surrounding the tumor and then the drug would be infused through an infusion pump through these catheters directly into the brain and into the brain tumor.

Chu That is pretty fascinating.

Baehring It is, it is called convection-enhanced delivery, and we were involved in one of the earliest clinical trials using this technique first in humans.

Chu That is interesting because there are these wafers that contain chemotherapy that are already approved for treating patients with brain cancer.

Baehring That is true. That was really the first concept where chemotherapy was directly administered into the brain, and Dr. Saltzman was instrumentally involved in the development of these wafers. These are dime sized discs, essentially, that are impregnated with the chemotherapy compound that is called carmustine or BCNU, and it is attached to the wall of the cavity that the surgeon creates when he takes out the tumor and then over the course of a few days, that chemotherapy drug diffuses into the normal brain surrounding the brain tumor and kills any tumor cells that were not removed at the time of surgery.

Chu It is fascinating, and it will be very interesting to hear more. We will have to get you back for a future show. Are there any clinical trials that you folks are involved with that you are particularly excited about?

Baehring We have a number of clinical trials and we have completed a couple of trials recently. One used a tumor-directed vaccine, essentially a vaccine that stimulates the immune system to target the brain tumor. Another clinical trial used one of those anti-angiogenic compounds that we talked about earlier, so a drug that interferes with a tumor's ability to form new blood vessels. Currently, we just launched a new trial in the setting of one of the national consortia, the Radiation Therapy

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Oncology Group, that uses the current standard treatment, which is radiation and a drug called temozolomide after surgery in conjunction with one of these to anti-angiogenic compounds, the bevacizumab or Avastin.

Chu Great. We look forward to having you back on a future show to hear more about the progress being made in the trial and all the exciting research that is going on with your group.

Baehring It would be my pleasure.

Chu Until next week, this is Ed Chu from Yale Cancer Center wishing you a safe and healthy week.

If you have any questions or would like to share your comments, you can go to yalecancercenter.org where you can also subscribe to our podcast and find written transcripts of past programs. I am Bruce Barber and you are listening to the WNPR Health Forum from Connecticut Public Radio.