

Welcome to Yale Cancer Center Answers with Dr. Ed Chu, I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center and an internationally recognized expert on colorectal cancer. If you would like to join the discussion you can contact Dr. Chu directly. The address is canceranswers@yale.edu and the phone number is 1888-234-4YCC. This evening Ed is joined by Dr. Jonathan Knisely. Dr. Knisely is co-Director of the Yale-New Haven Gamma Knife Center and an Associate Professor of Therapeutic Radiology.

Chu The topic for tonight's discussion is brain cancer. Can you give us a general definition for what brain cancer is?

Knisely Brain cancer, colloquially speaking, is cancer that involves the brain. Just as we can talk about cancers arising within the brain there are cancers arising elsewhere that spread to the brain and we need to be clear about the differences between those types of tumors. As we are talking about brain tumors, you can have primary brain tumors that are infiltrative and very difficult to treat, and you can have brain tumors that are sort of near the surface of the brain and much more readily treated.

Chu Primarily focusing on tumors that arise from within the brain, I gather there is a whole number of different types of brain tumors, brain cancers.

Knisely That is right Ed. The most common type of brain tumor is called the glioma, and glioma tumors arise from the support cells of the brain, not from the neurons themselves, but from the cells that help support the brain's activity. There are a number of different types of tumors that fall under the classification of glioma; astrocytoma, oligodendroglioma, ependymoma, and you can have mixes of those three types of tumors. Probably the most common type of primary brain tumor that we see in adults is glioblastoma multiforme.

Chu To give our listeners a sense, about how many new cases of say the last type, glioblastoma multiforme, would you say are diagnosed each year in the United States? Is it a common relative to some of the other cancers like breast cancer, prostate cancer, or colorectal cancer?

Knisely No, it is not common relative to some of the other cancers. Obviously smoking and carcinomas arising from bronchi, breast cancer, and bowel cancer are the big killers; the killer bees. But brain cancer is a big killer as well, in part because we have had such a difficulty in getting good control of brain tumors. The number of brain tumors that arise each year is probably about 7 per 100,000.

Chu What is the most common age at which brain cancers are diagnosed?

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- Knisely They are most commonly seen in people between the ages of about 50 and 70. As we have improvements in general health, people not dying of cardiovascular or hypertension-related problems, diabetes is better controlled, and people are living longer, so brain tumors are becoming more frequent.
- Chu That is interesting. Obviously brain cancer has received a great deal of attention recently with Ted Kennedy's diagnosis of brain cancer. Do you know what specific type of brain cancer Kennedy has?
- Knisely What I know is from the news media, and it has been reported that he has a glioblastoma multiforme.
- Chu What would be the main risk factors for someone developing brain cancer?
- Knisely I think the most common risk factor for most people is just bad luck, but there are some things that have been shown to be associated with brain cancer, such as a history of having had radiation in the past. For example, there are people who have had radiation for a pediatric malignancy, and they also use to use radiation for tinea capitis, a fungal skin infection of the scalp, and that led to a high instance of brain tumors in people who were cured of their fungal skin infection. There have been increased incidences seen in people who are electrical workers, people who have exposure to chemicals such as farmers, but the only thing that has been seen in series after series is exposure to ionizing radiation.
- Chu And is there a genetic component to brain cancer?
- Knisely There are some kindred, some families, which do have a higher propensity to develop brain tumors. Some of these are well characterized, others of them geneticists are still working out the details, but most commonly it is a sporadic thing in the patients that will be diagnosed.
- Chu There has also been a lot made in the press lately about reports of association between the use of handheld cellphones and brain cancer. What is your sense, is that myth, fiction, is there some truth to that?
- Knisely I have to rely on the reports of epidemiologists because obviously for somebody who has used a cellphone, did they use it more on the right hand side of the head or the left hand side of their head? And people got brain tumors before there were cellphones. I do not think that there has been a dramatic uptake in the incidence of brain tumors since cellphones became commonly used.

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- Chu Very widely used. It is really quite remarkable these days.
- Knisely It is hard to believe we did not walk around without them 10 years ago.
- Chu That is right. What are some of the common symptoms that might make one suspect that perhaps there might be something going on in the brain?
- Knisely The two most common general symptoms are headache and seizure. Headaches are most commonly seen in the morning, you might be awakened with a headache or wake up in the middle of the night with a headache. Seizures, of course, are uncontrolled electrical activity in the brain that leads to loss of control or abnormal sensation. The brain, however, is a very complex computer, to draw on an analogy to modern technology, and if one part of the computer is not working right it can affect a different part of the brain's function. A tumor arising in the part of the brain that is responsible for movement or coordination will affect those specific areas. One that arises in the area of the brain that is responsible for language will affect the ability to speak clearly, or come up with words. The most common thing that people initially might think about if they are having some of these problems is, "I'm having a stroke," or some sort of problem of that nature. Then being evaluated by a physician who has an adequate level of suspicion, getting a good examination, and getting imaging done to take a look at what is going on inside the head, are critical to help make the diagnosis.
- Chu If anyone should have any of these symptoms that you just mentioned, headache or maybe weakness or numbness or funny sensations within the arms or legs, who should they seek medical attention from first, should it be the general internist or should they go to a neurologist?
- Knisely I would say the internist is probably the best gatekeeper. Neurologists obviously have great skill at doing a neurological examination and may have a broader differential diagnosis. Unfortunately, most of the patients I see have brain tumors, so that when I hear hoofbeats I think of brain tumor, but there are lots of other conditions that can cause problems with the brain's functioning; vascular problems or problems with stress. I think an internist is the first person that should be seen to try and workup a problem that you suspect may be related to a brain tumor.
- Chu That is an important point to emphasize to our listeners out there. Should you have any of these symptoms that Dr. Knisely has outlined for you, probably the most common cause for those symptoms would be a benign cause, a non-cancer etiology.

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- Knisely It is also possible that you have medications for other conditions that may be causing problems. For example, for blood sugar, or you might be taking medications that are making you excessively drowsy or you are having a bad reaction. Obviously your internist will know what you are taking and what might be the guilty agent.
- Chu Say an individual goes to see their internist, the internist does the physical exam and finds some abnormalities, what would then be the next step in the workup process?
- Knisely The quickest and easiest test to get is a CAT scan. A CAT scan can be obtained in about 10 or 15 minutes time and will show whether there is a clear abnormality evident within the brain substance, within the brain tissue. If something is seen on that then it is frequently followed up in short order with a MRI scan. It is possible that a CAT scan would not discern, would not be able to make out clearly exactly whether or not something is abnormal. If that is the case and the symptoms are persisting or worsening, obviously an MRI scan has a more sensitive instrument and will be able to help resolve with a greater degree of clarity exactly what is going on.
- Chu One of the things that people have described is that if they are claustrophobic they might have difficulties getting a MRI, what is your experience with patients?
- Knisely I think the apprehension is the worst thing. Patients can get adequate amounts of medications like Valium, Ativan or Xanax that will make them drowsy enough that they will be aware that they are having the MRI scan, but the unpleasantness, or the subjective unpleasantness, of being within the MRI scanner is not so bad. There are open MRI scanners as well and those open scanners are certainly very good for helping make the diagnosis. The pictures are perhaps not as clear as might be required for some interventions like guiding a surgical biopsy, but in terms of making a diagnosis, you should not let concern about having an MRI scan stop you from getting the appropriate investigations to guide your diagnostic workup.
- Chu Great. Then what happens if, for instance, a mass, lesion, lump, or something abnormal is seen in either the MRI or the CAT scan, what would be done after that?
- Knisely A referral to a neurosurgeon is appropriate. Obviously we do not necessarily know exactly what it may be. There are benign causes, there are malignant causes, but obviously having any sort of a lump in your brain, particularly if it causing symptoms for you, one of the things that will most rapidly clear those symptoms up will be getting rid of that lump. Neurosurgeons are very highly skilled at working in and around the brain and they are the ones who would be able to ascertain what approach would be appropriate for taking out a brain tumor and what risks might be associated with that.

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Chu How invasive is the initial biopsy of that lump?

Knisely You can obtain a diagnostic biopsy with the introduction of a needle into the brain. An incision is made in the scalp, a small hole is drilled in the skull, and then a needle the size of a pencil lead, literally, is introduced under very precise imaging guidance to the point where the tumor is in order to find out what kind of tumor it is. This is something that could even be done as an outpatient, although most patients stay in the hospital overnight.

Chu Once a diagnosis of a particular kind of brain cancer is made, how is the decision made to proceed with a particular treatment?

Knisely At Yale Cancer Center we review all biopsies in a multidisciplinary conference. We have imaging experts from neuroradiology, we have neuropathologists, neurosurgeons, radiation oncologists, medical oncologists and neuro-oncologists, along with ancillary staff, social workers, and research staff to help review and chart a recommended course of action. Some of these tumors are clearly managed with a certain approach because we know it works so well. For others there are controversies about what approach should be taken. Are the risks associated with surgery acceptable? If the patient is too frail to undergo an aggressive surgical treatment, what should be done? Sometimes there are questions about the sequencing of treatments as well and we want to try and make sure that all points of view are considered before taking any steps that may have significant impact upon a patient's health.

Chu Let us talk more about the various treatment strategies on the other side of the break. At this time we are going to take a break for a medical minute. You are listening to Yale Cancer Center Answers and we are here this evening discussing the approach and treatment of patient's with brain tumors with our guest expert Dr. Jonathan Knisely.

Medical Minute

The American Cancer Society estimates that in 2009 there will be over 62,000 new cases of melanoma in this country and about 2400 patients will be diagnosed here in Connecticut alone. While melanoma accounts for only about 4% of skin cancer cases, it causes the most skin cancer deaths, but when detected early melanoma is easily treated and highly curable. Clinical trials are underway at federally designated comprehensive cancer center such as Yale Cancer Center to test innovative new treatments for melanoma. Patients enrolled in these trials are given to access to newly available medicines which have not yet been approved by the Food and Drug Administration. This has been a medical minute and you will find more information at [yalecancercenter.org](http://www.yalecancercenter.org). You are listening to the WNPR Health Forum from Connecticut Public Radio.

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- Chu Welcome back to Yale Cancer Center Answers, this is Dr. Ed Chu and I am here in the studio this evening with Dr. Jonathan Knisely, co-Director of the Yale-New Haven Gamma Knife Center and a senior member of the Yale Brain Tumor Center. Before the break we were talking about this multidisciplinary team that you are an integral part of that evaluates, assesses, and gives treatment recommendations for any patient who presents with brain tumors. For those who may have missed that discussion earlier, could you briefly review again what that multidisciplinary team does and how you go about making your recommendations?
- Knisely We review all the relevant information. Somebody who has examined the patient and has taken a history will provide the pertinent details of how the patient presented and other relevant medical facts. We will then review the imaging and if a biopsy has been done we will review that. After a biopsy has been done, if a surgery has been recommended, we will review the larger surgical specimen, the completeness of the resection that was achieved, and a recommendation will be made subsequently about management in order to try and optimize the patient's health. The recommendations frequently involve both chemotherapy and radiation therapy after surgery is done. There are some tumors for which radiation alone is used. There are some tumors for which chemotherapy certainly plays the predominant role in managing the tumor and knowing exactly what you are dealing with is of critical importance in order to try and optimize the management recommendations. We use different approaches for different tumors.
- Chu In general though, it sounds like there are three main treatment approaches that one can take for brain cancer, is that right?
- Knisely I explain to my patients that there are three ways we can treat cancer. One is surgery, which is kind of like using a paring knife on a potato and you want to get the bad spot completely out of the potato. Chemotherapy, which you know a lot more about than I do, and I think of as being a whole body treatment. And radiation treatment, which is a regional treatment where we can treat the area that is at highest risk of having progression of tumor. As a regional treatment we can treat some of the normal tissues at the same time we are treating the tumor in a way that a surgeon may not be able to in terms of excising the lump.
- Chu In a general sense, ideally, if it is possible to remove the tumor out of the brain and then follow up with either radiation +/- chemo, that might be the optimal approach.
- Knisely We certainly think that is true for brain tumors. There have not been any randomized trials where we take out part of your brain tumor and then give you radiation or chemotherapy, or we will take out your entire tumor and then give the radiation chemotherapy. But there is

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good evidence, what we would call class II evidence, that the more complete a resection the greater the likelihood of long-term durable control of a brain tumor.

Chu Jonathan, one of your specialties is in the use of gamma knife. Can you tell us what that involves?

Knisely Gamma knife is a brand name for a particular device that can focus radiation to very small volumes and give very high doses in a single treatment. I actually got into radiation oncology because I saw that with our ability to perceive exactly where a tumor was in three-dimensional space, and our ability to develop radiation plans to deliver radiation more precisely to the tumor, we would be making great advances in radiation oncology; and radiosurgery is that taken to an extreme. Radiosurgery involves, for the most accurate treatment, the placement of a neurosurgical halo, which is a device to immobilize the head and the brain within the head, and then an imaging study where several imaging studies are done to help clarify exactly where inside the skull, and where in relation to that halo or frame, the tumor or tumors are located. We then use a specialized computer program that can figure out exactly how to aim radiation just at the spot we want to zap. We go through a process of making sure that everything is going to be aimed exactly where we want it to go and that there will not be any problems delivering the treatment. We plan it all in virtual reality and we bring the patient in the same morning and we deliver the treatment, then the head frame is removed and the patient goes home. The closest experience I have had to that is going to the dentist and having some work done on a filling where you get numbed up. They attach things to your head and it is unpleasant for a few hours and then you get up a little bit sore and you go home.

Chu My sense is that what the doctor offers is probably a little bit more painful than this gamma knife procedure.

Knisely We have neurosurgeons that are very skilled at the administration of local anesthesia. The frame is put on with the use of Novocain to make sure that it is no more uncomfortable than absolutely necessary.

Chu With the gamma knife it sounds like there is no direct invasion; there is no cutting of the brain. That is really remarkable.

Knisely The gamma knife concept was originally thought up by a neurosurgeon who back about 50 years ago was worried about the appropriateness of doing open operations in patients when there were no intensive care units or other ways of ensuring patient's safety. If a

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neurosurgeon is going in to remove a lump, if we can destroy that lump and have the body clean it up much like a bruise or just be reabsorbed, the advantages are great. We think it is a great way to approach spots that should not be there, and keep them from becoming problems for patients.

Chu Who would be the ideal patient for whom gamma knife would be the preferred treatment of choice?

Knisely We want to have a patient who has a relatively small spot that is relatively discrete. By that I mean that we can clearly see where the edges of the tumor are. If the tumor's edges are beginning to infiltrate into normal brain tissue, or are too close to some very important structure, we will not be able to use a very high single dose of radiation. We would want to try and treat with an approach that would use smaller doses of radiation given in a repetitive fashion. It is best if the tumor is not more than about 3.5 cm in diameter. We want to try and treat patients before they become too symptomatic, because if there is any swelling associated with the treatment the symptoms that they may have may become a bit worse and they may need to take some steroids, medications like dexamethasone or Decadron, for a few weeks in order to try and control those symptoms.

Chu How would you compare the side effects, secondary to gamma knife, as opposed to the usual radiation treatments that are given to patients?

Knisely The focused nature of the radiosurgical treatment, and the fact that normal brain cells are getting such a small dose of radiation relative to the tumor, means that side effects are much less, associated with radiosurgery. Fractionated radiation therapy, the kind of treatment that may take several weeks to deliver, involves a lot of normal tissue at the same time the tumor is being treated. Although those normal tissues can withstand a certain amount of radiation, we know that there are side effects for those normal cells. The fatigue, loss of appetite, hair loss, and change in sense of taste that are commonly seen, for example, when we are giving radiation treatment to the brain for a tumor that could not be treated with radiosurgery, those are almost never associated with radiosurgery.

Chu That is terrific.

Knisely I frequently tell people that if it were my head, I would choose radiosurgery.

Chu Suppose a patient who had a diagnosis of brain cancer received the traditional radiation therapy, then, unfortunately, develops a recurrence in the same area where they had radiation

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therapy.

Knisely Gamma knife can be repeated. This is something that can be done on more than one occasion. The focal nature of it is almost like picking off something with a rifle using a scope for very precise aiming. So if you had had a spot that was treated on the left hand side of your head, and had one come back an inch away, the amount of radiation that was delivered an inch away was low enough with the radiosurgical procedure that we can go back and treat it again. We have patients, for example, with brain metastasis that have had metastasis treated on three or four, even five occasions.

Chu That is terrific. Do you ever think about adding chemotherapy after someone has had say gamma knife procedure?

Knisely We think that for brain metastasis, and I am speaking here specifically about brain metastasis as opposed to other types of tumors such as meningiomas, pituitary adenomas, acoustic neuromas, or schwannomas, that they do not develop if you have control of the tumor elsewhere in the body. They spread to the brain through the blood stream, and if we are treating the brain we emphasize to all our patients that we want to have their medical oncologist doing their absolute best to try and prevent new spots from developing. That can include going on to a different chemotherapy regimen, or perhaps being enrolled in a clinical trial if the standard management has not been shown to be successful for that tumor. One of the good things I would like to emphasize about radiosurgery is that there is very little impact upon the ability to receive systemic chemotherapy. We are not irradiating much of the circulating blood and the fact that this treatment can be done in a single day will mean that a patient who needs chemotherapy can resume their treatment promptly. There is no several-week delay while you receive radiation therapy and then have to recuperate before your chemotherapy can recommence.

Chu Another question for you Jonathan, we hear the term Cyberknife; is that the same or different than gamma knife?

Knisely It is a tool that is able to do many of the same things. It was invented by somebody who studied with surgeons that invented the gamma knife. Instead of the approach that the gamma knife uses where as many as 201 radiation beams are all aimed at the tumor at one time, the Cyberknife aims one beam sequentially for many different directions. It seems to take a bit longer to do the work, I have no experience with using it, but it is a powerful tool and obviously there are things that the Cyberknife does better than the gamma knife and there are things that gamma knife does better than the Cyberknife.

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- Chu Very quickly, it is amazing but we are nearing the end of the show, if anyone wants to access help or get information about the Yale Brain Tumor Center, is there is a contact person or a number?
- Knisely I would like to give two numbers out that are both 203 area code numbers. One is the brain tumor center proper, and you should ask for Betsy. Her phone number is 737-1671. If there are questions about the gamma knife, that number is 688-4040 and you should ask for Linda.
- Chu And of course for further information people can also access the Yale Cancer Center website, yalecancercenter.org.
- Knisely That is an excellent resource.
- Chu Jonathan, in the last 30 seconds that we have, are there any words of wisdom that you would like to convey to our listeners out there?
- Knisely I hope everybody is staying warm and I want to wish everybody a happy Chinese New Year.
- Chu I agree and we look forward to having you come back and hopefully we can talk about some of the research that you are involved with at the Yale Brain Tumor Center.
- Knisely That will be great Ed.
- Chu You have been listening to Yale Cancer Center Answers and I would like to thank my guest Dr. Jonathan Knisely for joining me this evening. Until next time, I am Ed Chu from the 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 programs. I am Bruce Barber and you are listening to the WNPR Health Forum from Connecticut Public Radio.