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Welcome to Yale Cancer Answers with doctors Anees Chagpar and Steven Gore. I am Bruce Barber. Yale Cancer Answers features the latest information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week, it is a conversation about brain tumors with Dr. Zachary Corbin. Dr. Corbin is an Assistant Professor of Neuro-oncology at Yale School of Medicine, and Dr. Chagpar is an Associate Professor of Surgery at Yale and the Assistant Director for Global Oncology at Yale Comprehensive Cancer Center. Chagpar Dr. Corbin, let's start by talking about neuro-oncology. A lot of people when they think about brain tumors are a little bit scared by the whole concept. Are we talking about brain tumors that start in the brain or brain tumors that start somewhere else and go to the brain?

Corbin That is a great question. Neuro-oncology is a discipline that actually takes care of both types of patients. Something on the order of 10-15% of all cancer patients may actually have a metastasis or a spread of their cancer to the brain, and in that case, that is a brain tumor although that brain tumor is part of a larger disease. There are another set of patients that we take care of, that have what are called primary brain tumors and those patients do not have evidence of cancer anywhere else in their body and actually the first sign of anything going wrong is something that happened in their brain.

Chagpar I know in a lot of cancers, whether it is breast cancer or thyroid cancer or all kinds of cancers that we talk about on this show, there are often different types of cancers even within one organ, is that true in the brain as well?

Corbin Absolutely. Talking with broad strokes -- there are multiple different types of cancers that occur within the head and the spinal cord. You can have cancers that involve the line of the brain, they are not really cancers – they are more tumors that involve the line of the brain and you can have cancers that involve different parts of the brain that have even different groupings, and so the most common type of primary brain tumor that a neuro-oncologist in general takes care of would be in a group of tumors called the gliomas and the gliomas grow out of the brain. We do not really completely understand where they come from but the thinking is that they come from a type of cell which is not the neurons or the sort of cells in the brain that specifically help with thinking and moving, but the type of cells in the brain that are helping the neurons to live and to function.

Chagpar Tell us more about these gliomas. What kind of tumors are they, how do they present, what is the prognosis?

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Corbin Gliomas have many different forms, and actually one thing that divides gliomas and many other forms of cancer is that we actually do not talk about gliomas in general, by stage. Gliomas uniquely do not spread outside of the brain. Very, very rarely they do, but most of the time even the most aggressive gliomas, which are called glioblastomas, they stay within the brain, they do not actually move to other parts of the body. So, the way that we generally divide gliomas is by grade, which is a different process and the main thing that defines grade is when a pathologist is able to look under the microscope after a surgeon has actually taken a part of that glioma out of the brain, then they can tell us what the grade is. However, speaking hypothetically about different grades of gliomas, there are four and grade 1 gliomas, the most common of which is a pilocytic astrocytoma, that one can be taken out and if it is completely removed by a surgeon, that patient we would not expect to have that tumor come back. And then, it moves all the way up to what is a grade 4, that is the highest grade tumor, which is a glioblastoma and a glioblastoma has a completely different prognosis, and unfortunately, that is a very aggressive tumor that is almost guaranteed to come back, not for every patient, but most patients.

Chagpar It sounds like when patients are diagnosed with brain cancers, it is really important that they understand what the grade is so that they understand their prognosis and treatment options.

Corbin That is exactly right. And then, as the field is moving forward and really this has happened over the past few years while I have been in practice, not only are we using the grade to help us with the way that we are treating the patient, but we are using other molecular characteristics of the tumor, and so a molecular characteristic is actually something that can be obtained by other testing, often not just by a pathologist with a microscope but by testing that is done in the lab and many of those tests are genetic tests, and so, in some ways you can think of it as the tumor has a genetic fingerprint and that fingerprint may actually change the recommendation for a tumor that has the same grade.

Chagpar So, this is the whole personalized medicine thing that we are always talking about on this show?

Corbin That is exactly right. And I think that that is the best example in neuro-oncology and that is the way that we practice in this era and that really has changed since I started training in neuro-oncology where previously it was really based on the way that the cells looked under the microscope. Now, treatment is really based at least for some patients, by one of those tests that are actually done frequently of a genetic basis.

6:32 into mp3 file https://cdn1.medicine.yale.edu/cancer/2018-YCA-0819-Podcast-Corbin_340979_5_v1.mp3 Chagpar When we talk about that personalized medicine piece, looking at the genetic or genomic components of the cancer, are we now talking about different kinds of chemotherapy to treat these brain tumors. Is that how things are personalized?

Corbin It has more to do with either the order of the treatments or the repetity with which we feel the treatment should be received or whether you should receive them together. I think one thing that would be good to make sure that everyone understands is the sort of usual treatment for some of these gliomas. It usually is divided into two forms. There is radiation treatment and there is chemotherapy treatment. And that is after surgical treatments are exhausted or they have elected not to do any further surgeries. So, radiation is administered by a radiation oncologist that we work with. Neuro-oncologists do not administer radiation themselves but we are often involved in the decision about when and whether or not chemotherapy is administered with radiation. And so, in addition to radiation, there are several different types of chemotherapy, some of which are given by infusion in an infusion center and some of which are given by pill. The most common chemotherapy that we give especially for patients with glioblastomas is called Temodar,that is a pill. However, there are some other chemotherapy regimens, the most common of which is called PCV, which is for the first initials of those drugs, and that is given at least in part with infusions. The molecular characteristics can tell us whether or not we should be giving one either PCV or Temodar or what our best guess is and whether we should be giving radiation and chemotherapy when the patient is diagnosed or whether we can give them one at a time or whether it is safe to watch the patient and decide. And by watch I mean, make sure that our patient does not have more symptoms, make sure that they do not have changes to their MRI before we decide to do other treatments.

Chagpar Let's start at the beginning now that you have mentioned symptoms, how is it that people present with brain tumors to begin with because one would imagine that brain tumors often present with headaches, but a lot of people get headaches, so how do you know that you are just having a headache versus needing a neuro-oncologist because you have a brain tumor?

Corbin That is great question. I think that a lot of our patients do have headaches. However, one of the things that I hear when I talk to the patients that is different from I think what a lot of people may think is the severity of a headache from a brain tumor is not the main issue. So, a severe headache is not helpful to tell you whether or not this is likely related to a brain tumor. Other patterns about the headache can be helpful. Headaches from brain tumors are sometimes worse in the morning. They are sometimes unusually constant or they may be different from a headache that a patient is used to having. And in addition and more importantly, it is the symptoms that happen other than a headache. So, tumors often cause problems with the brain that

10:00 into mp3 file https://cdn1.medicine.yale.edu/cancer/2018-YCA-0819-Podcast-Corbin_340979_5_v1.mp3 they are involving and those problems can be as different as the parts of the brain that control those either movements or thoughts or feelings. So, one of the issues is that sometimes people have numbness of an arm or a leg and a headache, they have weakness of an arm or a leg, they may have problems with their vision. It is anything that the

brain does that is involved with the tumor that actually is part of what the first sign for someone is. And that actually brings up one of the things that can be challenging about our patients coming to see us, is that frequently and this is something that is shared between brain tumors and other neurologic diseases, frequently the patients who have symptoms of a brain tumor, their symptoms are actually the absence of an ability to do that, and providers or other doctors can call that a negative symptom and it tends to be that the patients do not necessarily think that negative symptoms are as severe. So, the most I think common positive symptom that would cause most people to go see a doctor would be chest pain, that is something you feel; whereas, a very common symptom of tumor that occurs in the back of the brain would be a loss of a part of their vision, and that for some patients is not as disturbing as for example pain. And so, that can affect our ability to see the patients as quickly as possible.

Chagpar If you have these kinds of symptoms, you have a headache, it occurs in the morning, it is pretty constant, you have never felt anything like this before, you are having some numbness and weakness or seizures or something, what is your course of action -- do you go and see your primary care doctor, do you see a neurologist, do you see a neuro-oncologist, what kind of workup is done so that by the time the patient sees you, you have got the information you need to make a diagnosis and to talk about treatment options?

Corbin I think one of the things, one of the disclaimers I want to say now is that a sudden change in neurologic symptoms, the most likely thing is not a brain tumor but actually a stroke. And so, a sudden change certainly within hours but even within a day is a medical emergency and the only place to actually have those symptoms evaluated would be an emergency room. So, you should go to an emergency room right away. The emergency room can facilitate the scans that may actually help us differentiate that from a brain tumor. However, the usual sequence of events, and I am glad you mentioned seizures, a lot of our patients do have seizures, although that is not always something that brain tumors cause before they come, before the patients are brought to medical attention. A patient who has a sign of some sort of change, a headache – as long as there is no emergency, it is perfectly reasonable for them to see their family doctor. The family doctor may actually do what is called a neurologic exam and actually find things that are different that they did not detect and that may trigger them to do a scan, and that might be enough information where a neuro-oncologist at

13:11 into mp3 file https://cdn1.medicine.yale.edu/cancer/2018-YCA-0819-Podcast-Corbin_340979_5_v1.mp3 a brain tumor center would be helpful. Frequently, they do not come to see neuro-oncologists first, frequently they get sent to a neurosurgeon and the neurosurgeon actually can also help with additional testing that may be necessary and sometimes either the neuro-oncologist or the neurosurgeon is the one who is called from the emergency room. So, it can be either way they come to us, and then the

neuro-oncologist is definitely most helpful after the diagnosis with respect to helping determine treatment. And then, I use this term, diagnosis, which is so important to oncologists, and oncologists often mean a specific thing when they say diagnosis, which is something that is different from what a lot of other either doctors or people in the public may think, and diagnosis is not the first sign of a change for example on a scan, but a diagnosis that we want to arrive to is really something we get from pathology.

Chagpar We are going to learn a lot more about the diagnosis of brain tumors and what we do to get a diagnosis and treatment right after we take a short break for a medical minute. Please stay tuned to learn more information about brain tumors and neuro-oncology with my guest, Dr. Zachary Corbin. Medical Minute

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This is a medical minute about breast cancer, the most common cancer in women. In Connecticut alone, approximately 3000 women will be diagnosed with breast cancer this year, but thanks to earlier detection, noninvasive treatments and novel therapies. There are more options for patients to fight breast cancer than ever before. Women should schedule a baseline mammogram beginning at age 40 or earlier if they have risk factors associated with breast cancer. Digital breast tomosynthesis or 3D mammography is transforming breast screening by significantly reducing unnecessary procedures while picking up more cancers and eliminating some of the fear and anxiety many women experience. More information is available at YaleCancerCenter.org. You are listening to Connecticut Public Radio. Chagpar This is Dr. Anees Chagpar and I am joined tonight by my guest, Dr. Zachary Corbin. We are talking about new advances in brain tumor treatments and clinical trials, and right before the break, we were talking about how patients present with symptoms that may be suggestive of a brain tumor. So, we talked about headaches and seizures and weakness and so on. Right before the break, one of the things you mentioned was that it is really important in terms of obtaining a diagnosis, an actual name of a tumor to obtain pathology. How exactly is that done?

16:18 into mp3 file https://cdn1.medicine.yale.edu/cancer/2018-YCA-0819-Podcast-Corbin_340979_5_v1.mp3 Corbin Excellent question. We work with our neurosurgical colleagues and there are many neurosurgeons who actually have a focus of practice in brain tumor surgery, and so, those are the ones with whom we work most closely and they really have a lot of impact on how a diagnosis is obtained especially in an organ like the brain where the location of the tumor has so much to do with the amount of disability it can cause, which could be permanent weakness and also it has so much to do with how much disability you could have by doing a neurosurgery to try to determine what the diagnosis is. And so, there are definitely some tumors that

we are only able to see the signs of on a scan, for example a magnetic resonance image or an MRI, and so we have to stop there because the neurosurgeon tells us it is just not safe to do a biopsy even, which is the medical term for sticking a needle inside of a tissue and not taking anything else out. But there are times in which a biopsy even is unsafe and there is a completely different setting in which there are parts of the brain where although they do important things, mostly would not notice a change even if you took a large portion of the brain out, and the most common area is one of the frontal lobes, for example. And so, you could have a very large tumor in the frontal lobe that if you remove actually it causes very few symptoms and so a surgeon would not even want to do a biopsy to begin with, they would want to have the patient have a full surgeon in OR where they actually even remove part of the skull and take out an entire tissue or entire tumor. And so, once we have as much of that as we can safely obtain, then we are able to get both the pathologist's perspective, what it looks like under the microscope compared to normal brain and then also that molecular fingerprint, which involves some genetic tests as we discussed. Sometimes the molecular fingerprint only tells us what we should or should not do for a certain type of tumor and sometimes it tells us different things, it moves what we are going to do from one treatment arrangement to another. I think one thing I would like to talk about is the most common diagnosis that we treat, although all of our diagnoses are rare officially, it is what we see most of, glioblastoma. And the patients who have glioblastoma actually have recommendation, assuming that everything is going well, for very aggressive treatment, and so the evidence shows that the patients do the best if they receive to begin with about a month after surgery both radiation and chemotherapy at the same time, which we call chemoradiation, for 6 weeks. Following that 6-week period, they have a month break and then they have 6 more months at least of just the chemotherapy. For example, for someone who has a diagnosis of glioblastoma and maybe they are not as interested in receiving all of the treatment as I have described it to you, our ability to counsel on whether or not that is advisable might have to do with one of those genetic signatures. There is a genetic signature that is called MGMT and that signature if it is methylated, it actually tells us that chemotherapy is really helpful for that tumor, it fights it well. And if it is not methylated, it tells us that chemotherapy

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is not as helpful for that tumor and some neuro-oncologists may actually say it is not even necessary as part of the treatment. So, that is a good example of what we think is a relatively common diagnosis, but actually one of the main treatment discussions can stem from those molecular features. And then furthermore, for example, at Yale, we have a trial in which a patient would only be eligible for one of the trials if they have that methylation of the MGMT promoter in their tumor. And so, in addition to helping us counsel patients on what the best way forward is as their doctor, we can also help counsel them as

clinical researchers about what treatment trial options there are.

Chagpar That is a nice segue to talk about clinical trials. What are the new or exciting advances in neuro-oncology because I will tell you, a lot of people who are listening may think, "oh! My gosh, brain tumor, that sounds like a really scary word," and are hopeful that it becomes less scary in the future with new treatments.

Corbin I think that hope is really shared by a whole array of researchers and clinical trials throughout the country. At Yale specifically, we have several different clinical trials that are available, and so one of the things to know about clinical trials I think might be the most important for patients and their loved ones is that clinical trials are often available for patients at diagnosis which is right when they had their pathologic diagnosis before treatment is started or at what is called recurrence, which is the sign that the tumor is back either because the patient is having a harder time or because the patient has changes on the tests that we have done. And actually, the clinical trials available to that patient would be different based on whether they are newly diagnosed and whether or not it is a recurrence and whether or not they have had various different treatments that happen along the way, which might actually impact their what is called eligibility for the clinical trials. I think some things that are exciting in neuro-oncology that are currently going on is whether or not something that has been really big in the headlines in cancer might help in neuro-oncology, and that is called immunotherapy. Immunotherapy as we use it in our trials in neuro-oncology is an antibody that actually blocks a cancer's ability to almost cloak itself from the immune system or block the immune system which is part of our normal body from actually targeting and killing the tumor. It turns out that it certainly does not work as well in the brain as it does in some other cancers – for example, the best example is melanoma. It works very well in a lot of melanoma patients. It certainly does not work that well in brain tumors, but there is actually a subset of patients where we have a lot of suspicion they may benefit from immunotherapy, and that is the kind of advance that we are really excited about. And there are other things actually that are sort of further away from the ability to treat a patient right now with it, but might advance our understanding of it, and that is something that I spend a lot of my time doing and that is metabolic imaging. So, one of the things that we have learned and we learned a long time ago but have revisited, is that cancers actually have different metabolism than the

24:04 into mp3 file https://cdn1.medicine.yale.edu/cancer/2018-YCA-0819-Podcast-Corbin_340979_5_v1.mp3 normal body the way that they use glucose, even if everything else is normal, can be different than the way that a normal body uses it. And so, we have had a really hard time in the past actually looking at the way that something like a brain tumor uses glucose and other metabolites because there is no picture that exists right now that we can show a patient that actually tells us that. The closest and what some really astute listeners might be thinking, isn't that what a PET scan shows me? I

thought that was a metabolic scan. It is true that some PET scans do show something about metabolism, but what they really do not show is how once glucose or another fuel gets to a tumor, how it is being used. So, we actually have several different techniques that we are working on that will show us potentially that change that happens within the tumor. And the reason why that is really important is one of the things we have not talked about yet is that - for example, if a patient has had a very aggressive treatment for an aggressive tumor, it is such an aggressive treatment that sometimes a neuro-oncologist spends a lot of time trying to determine if the tumor is back or if what we see is called pseudo-progression. And pseudo-progression is a funny sounding word for reaction. So, your body reacts to things that have toxicity to them or can damage the body, and radiation and chemotherapy do both of those things and we have a lot of patients whose brain is really reacting to our treatment. And so, one of the things is we have no scans for example now that are particularly helpful with determining the difference, and I think it makes sense to a lot of people – well, if the body is reacting to the treatment, maybe we should keep doing what we are doing because the tumor is not there. Whereas, if the tumor is clearly there, for example if there is a metabolic signature of a tumor that is different from a metabolic signature of reaction, then maybe that would help us in the future as well. We are not ready to treat patients, but we actually also have patients do research MRI scans where they are helping us learn whether the tools we have to see those metabolic signatures, which are sort of different from the molecular signatures we were discussing before, may help neuro-oncologists in the future with patients who have brain tumors.

Chagpar That brings up a question that I think a lot of patients sometimes have, which is, we talk a lot about tumors eating glucose, so is having a high-sugar diet a risk factor for getting a brain tumor?

Corbin That is a really great question. I recommend all my patients continue to have a healthy and a well-balanced diet. There are certainly some diets called elimination diets that patients may want to take to reduce the ability of the tumor to grow or maybe even with your question of a risk factor reduce their risk of having a tumor. But most of the time, we do not recommend those elimination diets. I do want to talk about risk factors though. Risk factor is a very common question that we get, and I think the biggest question maybe in everyone's mind is does my cell phone cause brain tumors? And in general, we do not think so. Actually, we do not think most people have a risk

27:44 into mp3 file https://cdn1.medicine.yale.edu/cancer/2018-YCA-0819-Podcast-Corbin_340979_5_v1.mp3factor for their brain tumor. When we see patients, very rarely do I think something clearly caused that brain tumor. There are a few exceptions. There are some genetic syndromes – the most common that I have seen is neurofibromatosis, types 1 and types 2. Those are both associated with gliomas, and in addition, there are a few others that are genetic syndromes. However, for someone who is for example 40 or 50 or 60, more than likely they would know they had that syndrome

for some other reason and the brain tumor would not be the first sign of it. So, in general, they are not genetically linked either. Because sometimes patients that we see say should my daughter get tested and that usually is not advisable. And then the other thing is whether or not there is radiation that the patient has been treated with. Now, small doses of radiation are not likely to be involved but a nuclear accident for example or if they have had a radiation oncologist before that has needed to treat a cancer that has already spread to the brain that is not a brain tumor, those patients do have higher risks. So, there are some patients that do have a higher risk, but that is a very rare patient. Most of the time, we do not have a cause for their brain tumor, which is another area of research.

Chagpar It sounds like there is a lot of really exciting research going on, just in our last 30 seconds is the prognosis for most brain cancers -- good, fair or poor?

Corbin The prognosis is really variable. There are some patients as I mentioned where you could actually tell them they do not need to come back and see you, they have been cured after they see a neurosurgeon who has done the best surgery they can and there are other patients that we establish really long-term relationships with and we tell them we need to see you anywhere from every once a month to every two months to once every six months. And so, in that sense, it is very variable and it is one of the reasons why neuro-oncologists can be really valuable to a patient and help them along their way. Dr. Zachary Corbin is an Assistant Professor of Neuro-Oncology at Yale School of Medicine. If you have questions, the address is canceranswers@yale.edu and past editions of the program are available in audio and written form at YaleCancerCenter.org. I am Bruce Barber reminding you to tune in each week to learn more about the fight against cancer here on Connecticut Public Radio.