Support for Yale Cancer Answers comes from AstraZeneca, working to change how cancer is treated with personalized medicine. Learn more at astrazeneca-us.com.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 the treatment of brain tumors with Dr. Nicholas Blondin. Dr. Blondin is an Assistant Professor in Clinical Neurology at the Yale School of Medicine and Dr. Chagpar is a Professor of Surgery at Yale. Chagpar Let's talk a little bit about brain tumors. I think brain tumors are one of those tumors that is really difficult for people to understand in the sense that there are tumors that start in the brain and then there are tumors that go to the brain. And those are two very different buckets, is that right?Blondin Yes and no.Chagpar Tell me about that.Blondin They are different in terms of them being a different disease, but any diagnosis of any kind of brain tumors are terrifying for a person and both types of tumors cause neurological disabilities, can really dramatically impact someone's life, and some treatment modalities could be similar between the two different types.Chagpar But certainly when you talk to your doctor about having a brain tumor, it is good for you to know whether this is a brain tumor that started in your brain or whether this is a tumor that went to your brain from someplace else?Blondin Yes, I would agree with that.Chagpar I want to keep our discussion pretty clean today and talk primarily about tumors that start in the brainBlondin That sounds reasonable. Those are called primary brain tumors.Chagpar Primary brain tumors. Tell us a little bit more about those primary brain tumors. What are the different types, who gets them, how common are they, that kind of stuff?Blondin Primary brain tumors are tumors that arise in the brain or structures that surround the brain. Brain tumors can be classified as benign or malignant. Benign brain tumors are most commonly meningiomas. Meningiomas are tumors that arise on the lining of the brain – the meninges, and they can grow inward and cause pressure on the brain 2:49 into mp3 file https://cdn1.medicine.yale.edu/cancer/2019-YCA-0217-Podcast-Blondin_351895_5_v1.mp3 resulting in symptoms. Other less common types of benign brain tumors would be a schwannoma or acoustic neuroma - that is a tumor that forms on the nerve that is used for hearing and there are some other very uncommon ones that can affect the eye and other neurological structures. For malignant brain tumors, the most common malignant brain tumor is called glioblastoma or GBM. Malignant brain tumors arise in the brain tissue itself and can cause destruction, essentially stroke-like damage or acquired brain injury and they can spread throughout the brain and cause disability in that manner. And there are less aggressive kinds of malignant brain tumors called astrocytomas, which progress more slowly or have a better response to treatment. In terms of who gets these, anyone can get a brain tumor. In fact, for children, brain tumors are the most common type of pediatric cancer. And there are a lot of efforts going towards treatment in kids these days. For adults, the incidence of brain tumors increases with age for benign brain tumors and for malignant brain tumors, also the risk increases with

age but there is less of a relationship, pretty much anyone can get GBM, from teenagers or children, out to people in their 90s. I have cared for patients that have pretty much run the entire gamut of ages.Chagpar How common is a primary malignant brain tumor, like a glioblastoma multiforme or GBM?Blondin Fortunately GBM is a rare cancer type. I think the incidence is around 3 per 100,000 people. So, in Connecticut, there will be approximately 100 newly diagnosed cases per year. The incidence is slightly higher in men compared to women. Again, it runs the full range of ages but it is most common in the 60s or 70s age population.Chagpar We talk a lot about how do you know when you might have a brain tumor. One would think that you would have symptoms, right; headache or something like that right?Blondin The most common symptom is actually a seizure. An otherwise healthy adult who has a first-time seizure likely indicates the presence of a brain tumor. Headaches on their own actually would not really be a common symptom of a brain tumor because migraine headaches or other benign headaches are a very common medical problem that people have, but headaches along with other neurological disabilities like weakness or memory loss or cognitive impairment – that could suggest presence of a tumor.Chagpar If you have a seizure and you have never had seizures before and you do not have epilepsy, that might be a good reason to go and see your doctor?6:01 into mp3 file https://cdn1.medicine.yale.edu/cancer/2019-YCA-0217-Podcast-Blondin_351895_5_v1.mp3 Blondin Yes. Seizures are very scary when they occur. Generally, EMS services are called and the patient is brought to an emergency room and there, imaging is done like a CAT scan that will look to see if brain tumor is present.Chagpar And so, what if it is, then what happens?Blondin At that point, further testing needs to be done. More advanced imaging like an MRI scan should be done to try to determine the exact place the brain tumor is, is it in the brain tissue or in the lining of the brain and then is this is a primary brain tumor or is it one of those secondary kind of tumors – like you mentioned caused from another kind of tumor in the body, so some other testing is done usually when they are hospitalized to determine what this could be and make a plan for some kind of biopsy or a surgery.Chagpar If somebody came in and had a seizure and they did a CT scan and it showed a mass and they did an MRI and it was in the brain, then they would go looking for another primary source – breast, colon, lung, thyroid, some place, and if they did not find it, would they think that this was a primary brain tumor and then do a biopsy of the brain?Blondin Yes, that's how the treatment plan would go. A neurosurgeon would be consulted and involved in the case and determine what kind of surgical procedure should be performed. So, in some cases depending on where the tumor is located, complete removal of the tumor could be feasible, and in other situations, only a biopsy could be done and in certain more rare situations like if the tumor is in the brainstem, no biopsy really can be safely done, but it is best to try to at least obtain tissue through a biopsy or resection to know for sure what the diagnosis is.Chagpar It sounds like these are often diagnosed with a surgical biopsy as opposed to a needle biopsy, is that right?Blondin Yes, it depends on the location in the brain where the tumor is I would say.Chagpar I guess when

we think about most tumors that we talk about on the show, we often diagnose this with a needle biopsy. I would think that the skull kind of gets in the way of doing a brain biopsy some of the time?Blondin It turns out, it is not that difficult for neurosurgeons to make a small hole through the skull. Chagpar True but for a needle? 8:30 into mp3 file https://cdn1.medicine.yale.edu/cancer/2019-YCA-0217-Podcast-Blondin_351895_5_v1.mp3 Blondin Right. If the tumor location is near the surface of the brain, there could be arteries or veins there which could be damaged by a needle. And so, doing a larger biopsy or resection where the surgeon can see with their eye where they are going, it is a lot safer approach.Chagpar Once a biopsy is obtained and you find out that it is a GBM, then what happens?Blondin At that point again, we confer with the surgeon and our multidisciplinary team with a medical oncologist or neuro-oncologist and neurosurgeon, radiation doctor, pathologist and neuroradiologist, we all look together at the case, see what was done, determine if more surgery should be done, determine if a complete surgery was done initially. Then, if that was the case, we would move on towards other kinds of treatment, generally radiation and chemotherapy, and again look at the molecular findings with the tumor and work with the pathologist on that to identify the optimal treatment strategy for a patient.Chagpar How do you know that chemotherapy is going to work in a patient? We have talked a little bit on the show about drugs not crossing the blood-brain barrier, and presumably, chemotherapy is given into the blood, so how does it get to the brain exactly?Blondin In glioblastoma or GBM, there is a big unmet need for new treatments. There are essentially only 2 chemotherapies that are FDA approved for treatment of GBM. The first treatment is temozolomide or TMZ. TMZ is pills that are taken, absorbed into the blood stream and then can easily cross the blood-brain barrier and go into the tumor cells. They damage DNA in GBM cells and can slow down tumor cell growth in that manner. Unfortunately, TMZ is not highly effective to treat these tumors, so the tumors often can have a resistance to them or have a recurrence, generally it is after several months of treatment, and the second chemotherapy is bevacizumab or Avastin that is a biological therapy that absorbs a hormone called VEGF that is involved in blood vessel growth around the tumors. So, the Avastin can slow down blood vessel growth and cause some shrinkage of the tumors, but tumors again can become resistant to it and then have subsequent regrowth.Chagpar What's the prognosis for GBMs given the fact that systemic therapy may be effective but only for a few months?Blondin The prognosis depends on a few factors – the most important of which is age for the patient. Older patients generally fair worse unfortunately. For someone in their 80s or really 70s and above, it may be less than a year of survival. For younger folks, it could be longer, could be out to like 2 years, maybe someone that had an extensive 11:47 into mp3 file https://cdn1.medicine.yale.edu/cancer/2019-YCA-0217-Podcast-Blondin_351895_5_v1.mp3 surgery and could respond to treatment, even 3 years. There is a molecular feature in tumors called MGMT status and tumors that have a certain kind of MGMT status are more responsive to treatment than the other kind, and that is an important kind of thing that can be used to give a patient prognosis, but it does not impact what treat-

ments they would receive these days.Chagpar It sounds like the prognosis is still not great with these primary brain tumors?Blondin We certainly have a long way to go. There is one additional treatment that has come along in the last several years– that's tumor treating field technology or alternating electrical fields. A device called the Optune system can be used by the patient where they wear these rays on their scalp that creates an electrical field which also can slow down cell division. It works in combination with temozolomide or TMZ chemotherapy, and patients can use that in addition to the chemo to try to get enhanced tumor cell killing.Chagpar Does it work?Blondin It increases the time until the relapse and overall survival of patients by a large clinical trial.Chagpar By how much?Blondin For newly diagnosed patients that received standard radiation therapy and the chemotherapy, usage of the device with TMZ increase progression-free survival a little under 3 months and overall survival of the patients by about 5 months, increasing from about 19 months to 24 months survival. So, on the one hand, I wish it was more time; on the other hand, compared to other cancer therapies giving a few more months is movement in the right direction. And there are certain groups of patients that seem to have even more benefit with Optune device than others, particularly again, this MGMT status – called MGMT methylated patients in the study did substantially better, increased survival almost a year for those patients.Chagpar What about the cost of the device?Blondin The device has a high list price, but patients can work with the company, generally insurances will cover it. It is not considered standard of care for treatment or NCCM category 1 to use the device with TMZ after radiation. So, much like any other cancer therapy, there is a high list price, but patients generally do not have to have a huge out-of-pocket cost to get the system.14:17 into mp3 file https://cdn1.medicine.yale.edu/cancer/2019-YCA-0217-Podcast-Blondin_351895_5_v1.mp3 Chagpar We are going to take a short break for a medical minute. Please stay tuned to learn more about treatment of brain tumors with my guest, Dr. Nicholas Blondin.Support of Yale Cancer Answers comes from AstraZeneca, providing important treatment options for various types and stages of cancer. More information at astrazeneca-us.com.This is a medical minute about head and neck cancers. Although the percentage of oral and head and neck cancer patients in the United States is only about 5% of all diagnosed cancers, there are challenging side effects associated with these types of cancers and their treatment. Clinical trials are currently underway to test innovative new treatments for head and neck cancers, and in many cases, less radical surgeries are able to preserve nerves, arteries and muscles in the neck, enabling the patients to move, speak, breathe and eat normally after surgery. 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. Nicholas Blondin. We are talking about treatment of brain tumors, and in particular, treatment of malignant primary brain tumors. Often, these are what is called GBMs or glioblastoma multiforme. These are aggressive brain cancers that start in the brain, often in older people. Nick, you were mentioning that the treatments that we have, we have a couple of forms of chemotherapy, we now have this device that might prolong

progression-free survival a little bit in these patients, the prognosis still is not great. And when we think about cancers of the brain and what they do, they take up space in the brain, they push on structures in the brain, when we think that there would be functional disability associated with having the cancer there, but also that there might be functional disability when people go in the brain and take chunks of it out or put drugs in there that cause effects in the brain or radiate the brain, so what about that functional disability?Blondin Certainly, the location of a tumor is a critical component. The brain has certain regions that control movement, sensation, vision, language abilities, memory, and it turns out there are some parts of the brain that really do not have critical functions. In particular, the frontal lobe of the brain or right temporal lobe of the brain often does not have critical functions for people, so tumors could arise in these locations, cause a seizure or some other kind of neurological symptom that lead to their discovery and then after surgery, the patient has really no neurological disabilities, and then in other cases if the tumor forms in the region where the motor neurons are, a person could have movement disabilities, stroke and that may not reverse after surgery. It turns out, a lot of this is just sporadic. It just happens where the tumor starts growing. So, it is never a fortunate thing to get a brain tumor, but if you were to get one, there are certain regions of the brain where it is much better for treatment than other areas.17:35 into mp3 file https://cdn1.medicine.yale.edu/cancer/2019-YCA-0217-Podcast-Blondin_351895_5_v1.mp3 Chagpar How does that play into decision making in terms of how aggressive to be with the treatment, what kind of treatment to go for – because one would think that after the decision to go through whatever therapy we are going to go through, whether it is surgery or chemotherapy or radiation therapy, those side effects from that treatment, the deficits for example feeling like you have had a stroke on side of your body, for some patients may be worse than the disease itself. How do you factor in the side effects of treatment and quality of life into decision making?Blondin That is what I believe is the most important part of my job as a neuro-oncologist. I look at a patient, what their diagnosis is, I know what all the standard treatments are and as we have discussed there unfortunately is not a huge number of treatments available, then I look at the patient, talk to them, talk to their caregiver, determine what kind of disabilities they have and what makes sense for treatment – how aggressive should we plan to be here with treatment. So, treatment can have side effects -- with radiation treatment, patients may experience fatigue, loss of appetite, feel run down; and with chemotherapy, patients could experience nausea, again fatigue and for some patients, those symptoms really could impair their quality of life, like if a person has mild disabilities but is still able to keep working, the patient may opt to not receive chemotherapy because they want to try to maintain some normalcy for their life for a period of time. So, I work with patients and determine what the best treatment is for them at that point. And obviously, things change over time; the disease could worsen, things may change and in some cases, things stabilize and the patients do well. I hold further therapy and we just kind of do monitoring with MRIs periodically to see where things are at. So, it has to be highly individualized

and certainly taken into account what the patient perceives quality of life to be, whether it makes sense to continue with aggressive treatment, whether we should pull back and think more about treatment that supports the patient and provides comfort for the patient and plan our care based on that.Chagpar The other aspect that I want to touch on is brain tumors in children because prior to the break, you said that brain tumors were one of the most common cancers affecting kids, when we talked about glioblastoma, we said that prognosis was 1, maybe 2, maybe 3 years and with the potential side effects of surgery and radiation and so on. What are the common brain cancers that occur in kids and the prognosis that they face?Blondin Kids, like adults, can experience both benign brain tumors and malignant brain tumors. For children the most common malignant brain tumor is called medulloblastoma. They occur in the back part of the brain, generally called cerebellum and they can cause difficulties with walking and other kinds of movements. They are generally picked up if 21:08 into mp3 file https://cdn1.medicine.yale.edu/cancer/2019-YCA-0217-Podcast-Blondin_351895_5_v1.mp3 a younger child develops balance problems. The treatment for them is variable. It depends a lot on the molecular features of the tumor. A lot of progress has been made in the last several years in terms of classifying medulloblastoma into 4 different types. A few of the types are highly responsive to treatment and patients can go into long-term remissions or be nearly cured, and other types are much more aggressive and do not respond well to treatment. So, medulloblastoma again is a common malignant tumor and another common type is called DIPG or diffuse intrinsic pontine glioma. That is a brain tumor that will grow in the brainstem of a patient and cause difficulties with movement and facial functions like talking, swallowing, eye movements. It is a highly disabling tumor that really does not have any standard of care treatment. It is known to be highly aggressive. Radiation is a standard treatment. There are a lot of clinical trials and research that is going on to try to determine better treatments for that disease.Chagpar How common are these in kids? I know that you told me that they are one of the most common tumors affecting children. Thank goodness, most children do not get cancer, but how common are they?Blondin I am not certain on the exact incidence. Again, they are rare in the general population, but amongst childhood cancers, they are one of the most common cancers along with leukemia.Chagpar Let's take a step back and say this, for most of the brain cancers that you have talked about so far today, with the potential exception of good forms of medulloblastoma, they all sounded like they had a pretty lousy prognosis, is that right?Blondin Again for benign brain tumors, they may be able to be removed with surgery.Chagpar Right. But for the malignant ones?Blondin Malignant tumors of medullary are difficult. They are generally felt not to be curable. The goal of our treatment is just put them into an inactive state and my goal is to keep my patients as functional as possible, make sure that the patient has the best quality of life that they can. There are some patients that have an exceptional response to treatment. With radiation, chemotherapy, Optune device or a clinical trial product, patients have exceptional outcomes. An example of this would be the first two patients that received the Duke polio

virus treatment for GBM, they are both still alive several years after receiving that treatment when they had a recurrent or relapse glioblastoma. In those 2 particular patients, that treatment worked. Then, for a number of other patients that were in the study, the treatment did not work. So, the 24:09 into mp3 file https://cdn1.medicine.yale.edu/cancer/2019-YCA-0217-Podcast-Blondin_351895_5_v1.mp3 hope is with every patient I treat initially that they will be an exceptional responder, that they will be one of the ones that has very long-term survival from GBM, and I think that is the best way to approach it at the outset. We do not know who is going to be the exceptional responder at the beginning of treatment, so I hope everyone is, and then you just go forward and you see where things go over time with treatment.Chagpar Where I was going with the fact that prognosis in general is not as good as we would like it to be, is really to steer our conversation more towards research and clinical trials because as we often talk about on this show, that is really pushing the standard of care and discovering new therapies that are better than what we have today. Tell us about some of the exciting research that is going on in the field and some of the clinical trials that are out there that might provide new hope for patients who have primary brain tumors.Blondin There is a lot of excitement in the field and there has been more recognition of brain tumors with notable individuals getting brain tumors like most notably John McCain recently passing away from GBM, so there is a lot of different types of products in development, something that I am pretty excited about is types of viral treatments like virus damage to tumors or viral gene therapy that can impact tumors. There are several products that are in development. I had mentioned the Duke polio virus treatment, which is still in a mid-stage of development. There is another product called Toca 511, which is in late-stage clinical development, in fact that trial has been run and results are hopefully expected next year. And there are several other viruses that seem like they could be promising in development. So, beyond that, there are also vaccines that are being looked into. There are several vaccine products and then other drugs to try to stimulate the immune system to attack the tumor, immunotherapy is becoming common with other cancer types, particularly lung cancer and melanoma. For brain tumors, understanding of the brain tumor immune system and immune microenvironment is ongoing. The currently available immunotherapy drugs are not very effective. They do not seem to be effective. Clinical trials are being done with those products, but more research is going into kind of next generation immunotherapy, and then there is a lot of hope that that strategy will be helpful.Chagpar I want to take this conversation back to the viruses. How exactly would a virus help us to kill off a brain cancer because most of our listeners when we think about viruses, we are thinking about either viruses that cause a cold or we talk a lot on this show about viruses that cause cancer like HPV. How does a virus actually fight a cancer?Blondin It turns out in GBM, the tumor secretes hormones and factors that turn off the immune system in the brain right around where the GBM is growing. In the rest of the brain outside of the GBM, the immune system still functions normally and the patient's body 27:16 into mp3 file https://cdn1.medicine.yale.edu/cancer/2019-YCA-0217-Podcast-

Blondin_351895_5_v1.mp3 of the immune system functions normally. So, if a surgeon injects a virus into the brain tumor, the virus can replicate and grow within the tumor, but then once it tries to spread into healthy brain or the bloodstream, their immune system can fight it off and knock it back. So, in that way, we can take advantage of the brain tumor - GBM being kind of this reduced immunity environment and have viruses replicate there, damage or kill brain tumor cells and then also stimulate the normal immune system to go in, recognize the tumor as a foreign substance and become activated against it.Chagpar So, the virus will replicate there because there is no immune system there, but then how does the immune system go in after the virus has replicated and gotten rid of the cancer, how does the immune system go in and get rid of the virus?Blondin Well, the immune system has ways to destroy viruses. If the virus goes into the bloodstream, the normal immune system should be able to hold it back.Chagpar So, even in that location say you have a GBM where the immune system is deficient in that area around the tumor, once the virus goes in they then start replicating, the immune system is going to know, there is virus in my brain, I have to go and kill that off.Blondin Yes, that is what is supposed to happen. Inflammation will come on in that area, in the region of the brain tumor and that can be beneficial and additionally kill tumor cells. It also could be a problem if it creates a lot of swelling in the brain and that can cause worsening neurological disabilities or make things worse. There is kind of Ying and Yang of immunotherapy or viral treatment to brain tumors.Dr. Nicholas Blondin is an Assistant Professor in Clinical Neurology at the 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.