



Brain Tumor Awareness Month 2017

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Welcome to Yale Cancer Answers with Drs. Anees Chagpar, Susan Higgins and Steven Gore. I am Bruce Barber. Yale Cancer Answers is our way of providing you with the most up-to-date information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week, in honor of brain tumor awareness month, guest host Dr. Howard Hochster welcomes Dr. Jennifer Moliterno for a conversation about the treatment and diagnosis of glioblastomas. Dr. Moliterno is an Associate Professor of Neurosurgery at the Yale School Of Medicine and Dr. Hochster is the Clinical Program Leader of the Gastrointestinal Cancers Program at Smilow Cancer Hospital.

Hochster Dr. Moliterno, can you tell us how you got interested in the area of neurosurgery and specifically taking care of brain tumors?

Moliterno First of all, thank you so much for having me this evening. I became interested in neurosurgery very simply. I always wanted to be a surgeon, although when I was young child, I was afraid of blood. So, my parents did not quite understand that, but nonetheless encouraged me to pursue what I wanted to.

Hochster So, you went into the field that had the least blood.

Moliterno Yeah, exactly. Well, actually I wanted to be a heart surgeon. And, I ended up with this. So, I overcame my fear of blood and I ended up not being too impressed with heart surgery.

Hochster It was not brain.

Moliterno It was not brain surgery, and so, when I was studying neuro-anatomy, I was fascinated how you could have a lesion in the brain or an abnormality in the brain and you could protect exactly where it was just based on having a good history and physical exam, and then I spent some time with the neurosurgeons and really was fascinated and enjoyed it. So, I put two and two together and became a brain surgeon. And then, while I did my residency training here at Yale, I was really drawn to the brain tumor patients. I think that it is a population of patients where you are seeing them at their most vulnerable and I would like to be there for them when they need me the most and so that is what drew me to that and in terms of the surgery, it is typically complex and challenging, especially for first certain types of brain tumors and so, that solidified my interest, then I chose to do some fellowship training at Memorial Sloan Kettering.

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- Hochster You did many years of surgical training and then neurosurgery training and then another fellowship in brain tumor?
- Moliterno I did seven years of neurosurgery training, and then one year of fellowship training at Sloan Kettering.
- Hochster After four years of medical school?
- Moliterno After four years of medical school.
- Hochster Well, we know you are well trained and very expert in dealing with these things. So, how do people usually show up when they have primary brain tumors? What usually brings them to medical attention and how do you usually see them for diagnosis?
- Moliterno Usually people are referred to me, most times after they have already presented to another doctor, and so, usually they will have some sort of issues whether it is headache or seizure or word-finding difficulties or weakness depending of course on the location of the tumor, and that will prompt them to be seen by their primary care physician or neurologist or eye doctor or even sometime they will be in a car accident and it can be incidentally found by chance, but nonetheless, they get to me and by the time they get to me, of course they are understandably scared because they have a new diagnosis of a brain tumor. They do not quite understand the diagnosis, and then of course they are to see a brain surgeon. So, usually they are not too pleased to see me at first and I try to change that as best as I can.
- Hochster That is a tough job.
- Moliterno It is.
- Hochster But, I agree that we often see patients and get to bond with them and have really wonderful relationships.
- Moliterno Absolutely.
- Hochster Are brain tumors, primary brain tumors, very common?
- Moliterno If you ask me, they are. Of course, because that is what I do day in and day out, but no, largely no, and the one thing to explain and to caution to people is everybody has headaches and everybody will have some vision trouble here or there and maybe just

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need glasses. So, this is certainly not to scare people to think that you know everybody walking around has a brain tumor. In the grand scheme of things, they are definitely relatively uncommon, but nonetheless, they do occur and we do see quite a few.

Hochster And more often one would tend to see something like either speech problems or weakness on one side or something that we would call a “focal neurologic finding” compared to personality changes?

Moliterno It really depends, and where the tumors occur, the location, so if there is a tumor that occurs in a location that we refer to as eloquent brain, which is a high functioning part of the brain, an area near speech and near motor which controls strength and near nerves that control hearing and balance and things like that, oftentimes the patient will present earlier with smaller size tumors because they will have as you said a focal neurological problem. It is when those tumors that occur more at the skull base or on the surface of the brain or in less dominant parts of the brain that can really grow to larger sizes and then they can have subtle personality changes or problems with cognition and that sort of thing, and so they can present like that for sure.

Hochster So, then somebody gets a brain CT scan and it shows an abnormal density or mass there?

Moliterno Correct.

Hochster But, you cannot necessarily tell if it is benign or malignant based on that.

Moliterno Somebody as you said will get a CT scan and then really the better test for understanding brain tumors is an MRI, and by the time they have seen me, they have already had the MRI and usually that is done with contrast which can help see whether or not there is any uptake of dye and again you know doing this day in and day out, we are fairly good at being able to have an understanding based on the characteristics if the tumor is benign or malignant, being more cancerous, and so I always tell my patients that I would like to be wrong and I hope to be wrong, but especially if I think that it is a malignant tumor, but I usually have a pretty good idea based on just the MRI imaging alone, but we do not know 100% until we actually have a piece of tissue if we need the piece of tissue.

Hochster And even the primary brain tumors, so called glioma type brain tumors, there are different categories in there?

Moliterno There are.

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Hochster And that depends more on what the pathologist sees?

Moliterno Correct, and nowadays, molecular testing as well and so there are four grades to brain tumors. We do not stage them like cancers of the body. It is grading and so grades I through IV, gliomas. IV being the most malignant, most aggressive, also known as glioblastoma. Grade II we refer to more as lower grade tumors, and so these have a more benign clinical course and what the pathologist sees usually is more benign as well, but there is always the risk there for transformation of tumors becoming higher grades such as the grade III, which is anaplastic and of course, grade IV GBM, and so that is why we still treat those very aggressively in terms of diagnosis and treatment.

Hochster And so, what is the treatment approach today for these kind of tumors?

Moliterno There are treatment approach here at Yale to be as aggressive as we can in terms of removing as much tumor as possible, but being as safe as possible and making sure that we maintain the patient's function, which of course is the goal of any surgery and so, often times, we will again see a patient after they have been diagnosed with an MRI, have a feeling as to what the tumor is likely and then if it is amenable to surgery, if we do think that it should be removed, again some tumors are found by chance and if they are benign, we can usually follow them, but further ones that were concerned about or the patient is symptomatic, etc., then we try to remove as much of tumor as possible, and we have certainly the resources and capabilities here to do that, as removing as much tumor as possible has been shown to be beneficial in terms of outcome.

Hochster So, the first thing will be this aggressive surgery, but still maintaining the neurologic functions.

Moliterno Absolutely.

Hochster To the best degree possible.

Moliterno Absolutely and so often times, we do get referrals where the patients have been told they have inoperable brain tumors for instance, and you know we see them and evaluate them and a lot of times, we can do certain things during surgery that makes the surgery safer that allows the tumors to become more operable. For instance, we have really sophisticated neuro-monitoring techniques, and so we are able to monitor motor function even speech if necessary with awake craniotomy, again not always, but when necessary that allows me as a surgeon to remove as much tumor as possible, but

be reassured that the patient's function is being maintained, so that allows me to really push the surgery as much as I can. Likewise at Yale, we also use intraoperative ultrasound as well as neuro-navigation, which is like a GPS system for the brain, which also helps in terms of as much tumor as we can remove and then of course we are the only center in the state that has an intraoperative MRI, and so the beauty of that is I can remove tumor, and you know as a brain tumor surgeon, I am pretty good at telling the difference between tumor, what is tumor and what is brain. Sometimes, it gets tricky even with microscope and so we can get a quick MRI with the patient asleep on the table, and it is the same quality as an MRI that is done in the outpatient setting, and so I can then go back and remove whatever tumor remains that I might have missed.

Hochster So, you have a magnet right in the OR?

Moliterno Exactly, there are two rooms. In the operating room and in between is a big magnet, is a big MRI, and it is on tracks on the ceiling and it goes back and forth between the two rooms and one of the rooms also is what we refer to as a hybrid operating room. It is the only one I believe, that has angiogram capabilities, and so that also allows us or I should say it allows my endovascular or vascular colleagues to do an angiogram at the time of surgery as well which certainly can make certain brain tumor surgeries especially ones that are particularly bloody. It can help decrease the bleeding and it also makes aneurysm surgery and other types of surgery like that safer and more effective.

Hochster You work with the radiologists?

Moliterno Actually it is a neurosurgeon. It is an interventional trained neurosurgeons.

Hochster I see. And so what is this magnet thing like? You put people through a metal detector before they come in?

Moliterno We actually have everybody watch a video before going into the MRI rooms and you have to go through certain training. Of course the instruments that we use are all metal, so they have to be at a certain spot away from the field. So, when it is time for the MRI after I remove the tumor, we will then count all the instruments, all the needles, everything that is metal.

Hochster I kind of assumed you use nonmagnetic metal.

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Moliterno No. The head frame that we put the patient in is nonmagnetic. So, there is a special one, but all the other equipment, not the anesthesia equipment, that is not metal either, but the surgical instruments all have to be put away, and counted, and so it is really quite an operation in the sense that there are many people who make these surgeries happen and just happens so effortlessly. It is pretty remarkable.

Hochster That is exciting. We are going to take a short break for a medical minute. Please stay tuned to learn more information about glioblastomas with Dr. Jennifer Moliterno.

Medical Minute

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It is estimated that over 200,000 men in the US will be diagnosed with prostate cancer this year with almost 3000 new cases in Connecticut alone. One in six American men will develop prostate cancer in the course of his lifetime. Major advances in the detection and treatment of prostate cancer have dramatically decreased the number of men who die from the disease. Screening for prostate cancer can be performed quickly and easily in a physician's office using two simple tests, a physical examination and a blood test. Clinical trials are currently underway at federally designated comprehensive cancer center such as Yale Cancer Center and at Smilow Cancer Hospital to test innovative new treatments for prostate cancer. The ARTEMIS machine is a new technology being used at Smilow Cancer Hospital that enables targeted biopsies to be performed as oppose to removing multiple course from the prostate for examination that may not be necessary. More information is available at YaleCancerCenter.org. You are listening to WNPR, Connecticut's public media source for news and ideas.

Hochster This is Dr. Howard Hochster and I am joined tonight by my guest, Dr. Jennifer Moliterno. We were discussing the surgical care of glioblastomas, high grade or malignant brain tumors. So, that sounds very fascinating about everything you do to try to get out every last malignant cell when you are operating on the patients who have these high grade brain tumors. So, what are some of the other treatments after you have done the best surgery that is possible?

Moliterno As I always tell my patients with glioblastoma in particular and even lower grade gliomas, we are usually able to get as much of the contrast enhanced portion or the portion of the tumor that takes up dye as much as we can, but these tumors tend to be

infiltrative and so there is usually microscopic spread of tumors that are beyond what we are able to see even in the best of circumstances anybody can see in the operating room and so it is very important that the patients undergo chemotherapy and radiation following surgery. Of course, it is helpful to remove as much of that tumor as possible as it makes the success of the chemotherapy and the radiation that much better.

Hochster And so, you work with a multidisciplinary team.

Moliterno Correct. And so, after surgery, usually the surgeries are tolerated remarkably well as most people are usually surprised, but most tend to spend a night or so in the ICU, couple of days in the hospital and go home. Of course, more complicated tumors in such may require little bit more rehabilitation, but following that, we will present the patient even after here she leaves the hospital, will present at our multidisciplinary tumor board where other doctors who are just solely dedicated to treating brain tumors, neuro-oncologists, neuro-radiologists, radiation oncologists, neuro-pathologists, etc. We will review each person and will come up with a plan, and that usually will involve especially for glioblastoma radiation and chemotherapy. Again, it is a very standardized protocol. The chemotherapy that is recommended which is given by the neuro-oncologist is an oral chemotherapy and it is usually tolerated pretty well by the patients. Of course, then there are options for clinical trials and such and being at an academic center with again this multidisciplinary type care makes us options more available.

Hochster What do you feel the advantages are of when you have these tumor boards, when you sit down with all these specialists including neuropathologists who spend all their day trying to classify the tumors as one of the I think key things in deciding the grade and therefore the prognosis?

Moliterno Absolutely, and so I personally would not work in any other type of environment and if it was my loved one, I would be sure to find a place and usually it is an academic place such as Yale that has such collaborative efforts amongst different subspecialists. These are people who including myself just dedicate our lives to treating people specifically with brain tumors and so that certainly an advantage for the patient and it makes real difference in terms of outcome, and I really could not do my job without the other people that I work with.

Hochster And, if you can take out the whole brain tumor, why do people need these additional therapies?

Moliterno So, you cannot take the whole thing out. As I mentioned, you can take out a large part of, if not even all of the part of the tumor that takes up dye. However, with gliomas in

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particular, they usually have cells that are spreading throughout the brain, and that extends beyond the area of the tumor that is taking up dye, and so, I always say no matter how good I am, no matter how good the surgery goes, there is always a role for chemotherapy and radiation with these tumors and it is because I, nor anyone can remove every piece of the tumor unfortunately. I wish that I could.

Hochster So, there is some kind of microscopic cells?

Moliterno Microscopic cells, absolutely.

Hochster That are infiltrating the brain tissue itself.

Moliterno Yes, and that is what the medications and the radiation really target. And so my job is still an important one because I decrease the tumor burden for sure and the more I can decrease the tumor burden, the less tumor there is for the chemotherapy and the radiation to work on.

Hochster And people usually recover pretty quickly after surgery?

Moliterno Absolutely, yeah. So, again, you know we tend to be referred the patients with more complex and complicated type tumors and so there are certainly exceptions that the patients can have longer recovery periods, especially if they have a more complicated type of a tumor, but by and large for the most part, the vast majority of our patients again have tolerated very well, have a very short hospital stay and go home, able to take care of themselves. I always say you know they come back to clinic around 10 days, 14 days after surgery and most of the time, I cannot even find the incision, you know to remove the stitches in such because hair has grown back. We only shave a small piece of hair and so people do remarkably well.

Hochster It is really great to hear. And then the course of this kind of postoperative treatment with the radiation and the chemotherapy, how long does they go on for?

Moliterno We usually will wait about two weeks or so before we allow the radiation doctors and the oncology doctors to start their treatment. We just want to be sure that the wound has healed and that sort of thing and then after that, the radiation is again pretty standardized, so about six weeks of treatment usually and then they will cycle that with the oral chemotherapy.

Hochster And how long does that go on?

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- Moliterno It usually goes on a regimen where they will come on and come off and the neuro-oncologist manages that.
- Hochster What is on the horizon that excites you for the treatment of these malignant brain tumors in the near future?
- Moliterno In terms of surgery, what excites me is the technology that allows us to push the surgery further, and so for me, that is again things like the intraoperative MRI, that is techniques in terms of neuro-monitoring, that is performing awake craniotomy when we need to monitor language which is not in every patient, but refining those things that make the surgery as successful as possible. In terms of trials, there is you know that is always on the horizon and clinical trials in terms of what we can do to better target the disease, as again it is largely not a surgical disease. There are limitations with what the surgery can do even in the best of circumstances. We are involved with a multicenter trial that allows a pretty benign and well tolerated drug that the patient will take and it converts it actually to a chemotherapy. So, it allows the patient to have less side effects, but of course the effects of the chemotherapy.
- Hochster So they need to take a pill to turn it on and kill them?
- Moliterno Yeah. I basically remove the tumor and then inject the virus into the resection cavity and that has an enzyme that converts the well tolerated drug into the not so tolerated chemotherapy right there.
- Hochster And the viruses go specifically to tumor cells and not the normal brain?
- Moliterno Correct, and then also kind of long the lines of surgery, every single brain tumor that we remove or even biopsy here at Yale, we send to our tumor bank and to our tumor labs and so not only do we as you were saying the importance of diagnosing the tumors properly, but we also look at the genetic makeup of every tumor, and so every tumor is sequenced and so we understand the mutation profile of all the tumors and I think that will play a large role in the future in better targeting these tumors. Glioblastoma for instance has many, many, many mutations, and so it is incredibly heterogenous and I think that is why chemotherapies have trouble with treating the tumor. So, the idea behind it and of course you refer to it as precision medicine is to more precisely target the mutations and the tumors with drugs that are more appropriate.
- Hochster Many of them have these IDH mutations.

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- Moliterno Yes, and so we usually talk about in terms of the lower grade tumors, but those are definitely important and so that is one thing we check for in terms of our markers and that helps with prognosis, but it also helps in terms of our decision making again at the tumor board.
- Hochster And the role of immunotherapy now in these gliomas, how is that?
- Moliterno And so that is another very promising avenue. Of course, taking a page from melanoma and from lung cancers and such and applying it to brain tumors has been incredibly important and so we have some of those trials here at Yale and the results have been quite promising and so that as well as small molecule inhibitors for instance I think that is where again as much as I like to think that a lot has to do with what I do and it does to an extent. It is really the medical treatment I think that is going to allow us to figure a way to cure this thing.
- Hochster But clearly what you do in terms of surgery and kind of reducing it to the minimum amount is really critical and helping people live the best for the longest time.
- Moliterno Absolutely, yeah. And not to mention that you know oftentimes these tumors, especially when they are larger, they can cause headaches for patients, they can cause swelling in the brain, they can cause problems too and so often times, I will take patients to surgery and they really do improve after surgery because that mass is gone and so I think there will always be a role for surgery and certainly for more aggressive surgery that is safe and that is the key making it as safe as possible.
- Hochster So, it sounds like we have a lot of technology that is going to play here and a lot of expertise where people really work solely on brain tumors at Yale Cancer Center. This is all different than people find in many places.
- Moliterno Yeah, I think it is certainly, and what you find at places like Yale, at Memorial where I was where you would expect it, but I think when we are talking in terms of brain tumors, I think it is important to be at an academic center such as the ones that I mentioned. I think people are sometimes reluctant when they hear academic because they think I do not want to be a guinea pig and I do not want you know have people practicing on me and you know whatever the myths are, but they are simply not true. What it means is that there are a lot of people collaborating to make it the best care possible.
- Hochster And so what is your advice to people when they unfortunately may find out that they have a brain tumor?

Moliterno My advice is seek care at an academic institution such as Yale. We are always happy to see the patients, always willing to see the patients and always consider getting a second opinion. Make sure that the surgeon you are seeing is somebody who is a brain tumor surgeon not just really a neurosurgeon who also does other types of surgery. You really want an expert. You really want somebody who is specialized in and again always seek a second opinion. It does not hurt.

Dr. Jennifer Moliterno is an Assistant Professor of Neurosurgery 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. You are on WNPR, Connecticut's public media source for news and ideas.