

## Diagnosis, Treatment, and Management of Medulloblastoma

Our webinar today will discuss diagnosis, management, and treatment of medulloblastoma. My name is Jillann Demes, senior program manager here at the American Brain Tumor Association. I'm delighted to introduce our speaker today, Dr. Fisher. Paul Graham Fisher is a professor of neurology and pediatrics, and by courtesy, neurosurgery and human biology, division chief of child neurology, and the Beirne Family Professor of Pediatric Neuro-Oncology. Dr. Fisher directs the brain tumor program at Stanford University. He is associate editor of the Journal of Pediatrics, and on the editorial board of Journal of Neural Oncology with his own research interest in the epidemiology of and clinical trials for childhood brain tumors. Thank you so much for joining us, Dr. Fisher. You may now begin your presentation.

Thank you so much. And I want to thank the listeners and thank especially the American Brain Tumor Association for providing this service. I'm going to go through a series of slides, and I'll try to keep it at a level that's understandable to people. What I want to do is talk about the diagnosis, management, and treatment of medulloblastoma, and I think the best way to do it will be talking just, at first, a little bit about how common medulloblastoma is, and then we'll go through three cases. No one case is typical, but we've taken one that's a child, which will affect many of the listeners. We talk a little bit, secondly, about infant or a baby with medulloblastoma, and then finally, the young adult.

Throughout this I'll try to focus on the management and then the treatment. We'll talk a little bit about newer treatments. We'll also talk about side effects and late effects of the chemotherapy and radiotherapy. And finally we'll close by talking about what is changing in the sort of categorization or risk factor stratification in this disease. I'm sure the listeners will have many questions about new molecular work going on in this field. But I'll move right into the slides.

So medulloblastoma is not particularly common until it affects someone in your family, it affects a loved one. It's about .7 out of every 100,000 children or young adults every year. Remember, there are about 3,500 adult brain – excuse me, 3,500 pediatric brain tumors each year, it's about 20% of childhood brain tumors. Pilocytic astrocytoma is more common, although most people will call medulloblastoma malignant and pilocytic low grade.

An interesting thing, which will come up later that's been known for years, more boys than girls are affected, yet girls have a better survival in this cancer, in this tumor. The average age or median age of diagnosis is around nine years, but there are some peaks and clusters around age three and nine, and then there's a trail of people over age 15 that are affected, about a third of the patients. The incidence, how common it is, hasn't changed over time. We don't think there is some change in the environment or something that's led to more or less of this tumor.

The tumor can show up in various ways. This slide shows a sideways view of the brain and the brain stem, and the back part called the cerebellum. Really the way to think about the brain, as the diagram shows, there's the cerebellum where medulloblastoma arises, and there's the brain stem right in front of it toward the nose. Sometimes the medulloblastoma comes out of the brain stem, as seen in the MRI on the left. Sometimes it's a little bit behind. There are some horizontal views here where you can see there's a round tumor in the second radiograph where it's in the middle. On the third you see two eyeballs upfront, and then you see sort of a circular mass over to the right side that you're looking at, that's another type of medulloblastoma. Sometimes, in the panel on the far upper right, medulloblastoma can be metastatic, have multiple spots within the brain. And then finally sometimes medulloblastoma will go along the spine in that lower right-hand corner, sometimes there the little white dots or what's often called metastasis or "sugarcoating" of the tumor.

For decades, really the last two decades, we've realized that there are probably some subtypes of medulloblastoma, and we distinguish them pretty much by what's under the microscope. The left-hand panel is what's called "classic medulloblastoma," sometimes the doctors call something called "small round blue cells." These are a little bit more purplish looking here. Sometimes you'll hear the term "nodular" or "desmoplastic," and we're going to come back to that term later in the call when we talk about categorization. And something that's come up, in the far right, recently over the last ten years, something called "anaplastic," where it's more angry, more histologically malignant medulloblastoma. They're all

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malignant tumors. They're all in what's called a "grade-four cancer." But even within that we know classic and nodular are a little bit better behaving than anaplastic, and we'll come back to that.

So the first case is probably a case that will resonate with a lot of the listeners. It's an eight-year-old boy who comes into an emergency department with about a month history of some headaches, particularly in the morning, and he has some vomiting, some falling, and then a day or so before coming into the emergency department he's unable to move his left eye to the side or what's called a "fixed nerve palsy." He starts having difficulty walking, sort of walks like he's taken something, but he hasn't. And, you know, this is a very typical presentation for a young child coming into the emergency department with medulloblastoma. It brings, up for the physician and the parent, what needs to be done from here. They go through the system pretty emergently.

I'm not going to go through all the details. I've provided – some of the slides have a little bit more text that the listener can look at more later at their own leisure. But, pretty much, I think the important point here in this massive text is to say a head CT is often the easiest, quickest way to go. It's an x-ray of the head. It takes about 10, 15 minutes. It can be done very quickly in the emergency setting. There's always a desire to get fancy things like an MRI, but we typically do that once the child is known to have a tumor and once the child is stabilized.

So in this story the child is found on the CT to have a mass in that high brain or cerebellum. The child's admitted to the ICU. And, yes, the MRI does, indeed, show it's a tumor that looks very suggestive of medulloblastoma, but an important point here, the MRI itself is not diagnostic. We're going to need surgery or a biopsy of some sort to establish the diagnosis.

When the MRI is done parents should understand, too, that it's very common, particularly this day and age to do a spine MRI at the same time. We do this because, two things, many tumors could be metastatic, we want to know if there are deposits. Secondly, we like to do it before surgery because sometimes immediately after surgery it's a little confusing what is postsurgical artifact or a blood product and what is true tumor. So it can get a little murky.

So in the management of this child, this child comes in, they're admitted to the ICU, and, as very typical, a neurosurgeon intervenes and does a great job. Typically, the children are placed on Decadron, or Dexamethasone, which is the generic name for Decadron. It's a steroid hormone. It makes the kids get a little bit sometimes ramped up or a little bit excited, sometimes some insomnia and sometimes a big appetite, which can be very hard because sometimes for the child who's in the ICU, they're not allowed to eat if they're getting a steroid. That said, the steroid is meant to decrease swelling in the brain. I always tell our patients and families here that the idea is like wringing a sponge and getting some of the water out. It's keeping it from getting too expansile.

Sometimes the spinal fluid in the head and the ventricles is blocked up because of the tumor, so a drain or something called a "ventriculostomy" is often placed, like in this child. And then the goal is to go ahead and remove the tumor relatively quickly. The goal for all pediatric neurosurgeons is what's called "gross total resection," meaning everything you can pretty much see by naked eye. There may be some small element left there, we'll come back to that. But gross total means largely everything is gone by the naked eye.

Importantly, when the surgery is done, tissues removed, it's sent for diagnosis. In this day and age, much of it is often banged for biologic studies. What will happen, and we'll talk about this at the end, some of it is going to be saved and sent off for molecular studies.

Just a passing note, too, and I'm going to get too detailed about this, but there has been shown in numerous studies now that children who are managed in this setting with a pediatric neurosurgeon versus a neurosurgeon who does predominantly adults, tend to do better. That said, the child still needs a neurosurgeon who is available readily and locally early on so that matter can be taken care of.

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This is a picture in this slide of what this child in the first case looks like. You can see there's a spinal cord coming up from the bottom of the picture in the middle of the brain stem. I'll use my mouse over here. And you can see this is the spine coming into the brain stem. And then this mass here that I'm outlining, this is the medulloblastoma here. This is what the surgeon's going to do. They're going to come in typically from the back of the head through a vertical incision, come in through the middle of the cerebellum and remove it that way.

So once that is done, then the work starts for the rest of the team. We'll talk about it later. Neuro-oncology is best practice with a team of people of various fields. The pathologist is essential because they'll make the diagnosis, in this case, of medulloblastoma. They look at it under the microscope, sometimes they do special stains called "immunohistochemistry," particularly to start understanding different subtypes of medulloblastoma that we're learning about.

After the surgery, most children recover relatively well, but some can have slowness in their recovery. In this case, this little child basically does very well. The surgery shows on MRI that the tumor has been removed, but the child then, a day or two later, stops talking. This happens in about a quarter of all children with medulloblastoma. It's something called "posterior fossa mutism syndrome." Most children it's shown by this talking for a day or two, but then suddenly no longer speaking. It can be very scary for parents. The children are often very up and down in their emotions. Their muscle tone is very floppy like a ragdoll. Their coordination may be very much off. And sometimes they have what are called cranial nerve palsies, meaning their eye movements are very out of whack, they're disordered, they move in directions they don't intend, or their face may be droopy.

As in this case, the MRI doesn't show any damage or anything that happened. There was nothing done wrong. There's nothing done wrong by the surgeon or the ICU or the team. This is something that happens, and happens more than we saw 20 years ago. It's thought to be some pulling and traction that sort of causes probably some temporary swelling in connections between the cerebellum, the brain stem, and other structures called the "thalamus," that's why the long word there, "dentatorubrothalamic," and that's what it's thought. But it's not meant to be that it's any damage. It's not something that could have been avoided or prevented. The sequelae of this usually get better with time, but in about half the children it's never a 100% recovery. Some kids it's 80% or 90% or 95%. Usually their speech becomes normal. Sometimes, though, their cognition is a little bit less. Their school skills and their thinking sometimes a little bit less than the outcomes of other kids with medulloblastoma. We'll talk about that in a moment with radiation.

Once this is done, you hear people always talk about staging. Staging for medulloblastoma means figuring out in the year 2014 which of two risk groups you're in. You're either average or you're high risk. There's no longer anything called "low risk." Average risk is a child who's had their tumor completely or gross totally removed. There's no evidence of it spreading elsewhere in the brain or the brain stem or the spine. And then the histology is one of those ones I mentioned earlier, under the microscope in a few years, classical or desmoplastic. They're high risk if they have dissemination. Dissemination means metastasis. It's either determined by the MRI of the spine, which is important to do, in lumbar puncture.

The lumbar puncture is typically done about 10 to 14 days after the surgery if the team feels its safe. But if the child has metastasis or an incompletely removed tumor or one that only had a biopsy, or we know if their microscopy, their micrograph shows that it's anaplastic, a more aggressive-looking medulloblastoma, then we call them high risk. The red point is getting to what I'm going to get at later.

In the future, we know that some of these features, like desmoplastic and anaplastic, actually correlate very tightly with what we now know are different molecular stratifications. So it's very clear with people that average risk and high risk are certainly the terms of the current era, although the physician community thinks that in the next probably three to five years we may have a different stratification more based in molecular roots of medulloblastoma.

So in this case the child is considered average risk. And this is where the whole work of the multidisciplinary team starts. It's not only oncology, neurology, and neurosurgery, it's also the other

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people that are certainly important, and that can be social work, child life, physical therapy, chaplaincy, a whole group, and it's very valuable for families. It's important that there's a discussion. Each institution does things a little bit differently, but it's very common to get certain points out very clearly early on. But the cause or the etiology for the tumor overwhelmingly unknown, and that's one of the things many parents are terrified that there was something they did or that they waited too long, and neither is true. There's nothing, even when their child comes in with metastasis, it's probably more the nature of the type of medulloblastoma than it is waiting too long.

The good news for parents to hear is that it is a relatively good survival compared to other cancers these days. Overall it's about 70% to 80% of children are cured five years out from the diagnosis. Most of the children are treated in children's hospitals. Many of them are what are called "clinical trials" or "protocols," often through cooperative groups. The most common cooperative group in the United States or North America is COG, Children's Oncology Group.

It's important to hear what are the potential side effects, both short-term and long-term, about the tumor, it's often a blur for parents when they're hearing so much information, but it's important to hear it and keep coming back to this. Most institutions will present the child through something called a "tumor board" or a "multidisciplinary neuro-oncology" conference where everyone can weigh in. The standard treatment for the child in this story is to give radiation to the head and the spine, and then a boost to the back part of the brain, the cerebellum, where the tumor is. A standard dosing here, 2,340, the old term "rads," currently term "centigray." And then the cerebellum, where the tumor was, is boosted up to about 5,580.

One of the things that will come up later I'm sure is the difference between conformal and proton beam. Conformal or conventional photons are what is used throughout most of the United States. There are now about ten centers using protons, which have a few theoretical advantages over photons for this tumor, maybe not as many advantages as in other tumors, but we can come back to that during the Q&A. Either one would be a standard treatment.

Following the radiation, chemotherapy follows. In the United States and throughout all of North America, and even large parts of Europe, the standard thing is to do a platinum drug, usually it's Cisplatin, and that's often paired with either CCNU, also known as Lomustine, and then often Vincristine. Sometimes people flop in Cyclophosphamide or Cytosine in place of CCNU. In average risk disease it appears that they're equivalent, and there are pros and cons of each approach. But that's the standard way of doing it.

One of the things that's important to say is that giving chemotherapy up front instead of radiation may not be the wisest thing to do. It can be done safely for a very short period of time. But if it's done over a long period of time sometimes the disease can come back and not be as controllable.

While the child's on treatment, it's very important to make close monitoring about a number of things, partly based on the side effects of the drugs. Platinum drugs, particularly Cisplatin, are known to result in ototoxicity or hearing loss. It's very common at most places throughout the United States that the child has hearing screening or an audiogram before each administration of Cisplatin. It's something where when there's change in the hearing, the doctor is then most often going to go ahead and make a change in the dosing of the Cisplatin, either by reducing the dose or sometimes stopping that drug entirely. Parents shouldn't be scared if the Cisplatin has to be stopped earlier than later. There have been a number of studies shown that for children who have reductions or stoppage because of ototoxicity it does not compromise their survival.

Vincristine is used a lot, and there's been debate in the neuro-oncology community about how much is necessary. One of the downsides of Vincristine are things like constipation, sometimes droopy eyes, but the most commonly seen is a neuropathy, which means the long nerves in the legs, sometimes children will get floppy feet or they have difficulty raising their feet on the floor and they can stumble. Sometimes, rarely, that can be irreversible, so we have to be very careful not to overdo it on the Vincristine.

Also while the child's on treatment, they go ahead and they keep being monitored not only in the clinic, but they get what are called "surveillance MRIs". Typically there's an MRI of the brain and spine about

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two to four weeks after the end of radiation, and then about every three months or every two cycles of chemotherapy.

Once therapy is all done, and that's a very hard time for families, very anxiety-producing, then MRIs to the brain and the spine continue every three months, typically until you're about two-and-a-half years from your diagnosis. Sometimes people will alternate spine MRIs. Some institutions, for instance, we do a spine MRI every time. There's no right or wrong answer. Then MRIs are done during years three and four at about every six months. By year five people go to either every six months or once a year, and then once a year thereafter.

It is important to monitor hormone status, neurological status, and then school function, neurocognitive function throughout this. Why, and we'll talk about this later, but radiation particularly can have injuries and effects on the brain. The younger you are, the more affect radiation will have on the brain, particularly children ages three to seven can have a drop in their IQ scores. They can have learning problems. And many children who receive radiation, not all, but many of them can wind up requiring special services or special education in school, some that will require 504 Plans and IEPs.

About 50% of kids treated, like this child, will wind up needing growth hormone. It's usually started a year or two after the end of therapy. Many of them will need thyroid hormone. They do need monitoring, as I mentioned earlier, for hearing and vision. And then one of the things the doctor community is increasingly recognizing, some of the children develop other tumors. The other tumors can be because the child was predisposed to tumors, or sometimes the drugs or the radiation we give can do that.

What if the child is high risk, the eight-year-old I described was average risk, but if they're high risk then we have to make a couple changes. The radiation amount is then 3,600 rads or centigray, not 2,340. And then we'll give boosts or additional radiation to any spots on the spine or the brain that has metastasis.

Sometimes the chemotherapy is altered, too. Sometimes they'll receive chemotherapy during radiation. Carboplatin is a drug that is used, sometimes Cytoxan or Cyclophosphamide. Sometimes people will add in other drugs like retinoids or retinoic acid. One of the other things that can be done in some instances, some children will undergo very high dose chemotherapy with stem cell rescue. There's some controversy about how effective that is or is not, but there is certainly a role for that in the discussion. And then there are other investigational approaches going on, sometimes through, again, COG, or sometimes through particular groups of institutions. In general, if it's something that's going to be an investigational approach, most doctors will recommend it's done on a trial, particularly one of the cooperative groups, either ones like Children's Oncology Group or Pediatric Brain Tumor Consortium.

Let me just turn briefly to two other cases, because these are going to be important to highlight just some differences and some other issues in medulloblastoma. Case two talks about a little girl. And so we typically talk about children under age three or four as infants or babies, although certainly three- and four-year-old children can be very mature. But this is a 14-month-old girl who comes in over a couple weeks with vomiting but no diarrhea. Like many children, she's initially considered to have reflux. Sees a gastroenterologist, but then somewhere along the way someone noticed the soft spot of her head is bulging, that she has a big head.

She winds up getting a head CT, again, because it's quick, it's easy. It leads to the diagnosis, and she has a medulloblastoma in her right cerebellar hemisphere. Well I said medulloblastoma, but all we know at this point is that she has a tumor. She, too, is admitted to an ICU. At that point, in a controlled setting, she's taken to the MRI scanner, brain and spine MRI with contrast called "gadolinium," and she's found to have a tumor in the cerebellum but not metastasis.

The next picture here you can see with the red and the yellow arrows, to the left side of the picture is the child's right cerebellum. There's this mass in the brain. And what's different compared to the other one, this is a medulloblastoma a little bit off to the side rather than in the middle. We know in infants, particularly in girls, this is often the desmoplastic side -- desmoplastic type. This is sort of the way they show up.

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So let's just talk for a moment about baby medulloblastomas. As I mentioned, kids under age three or four, the treatment approach is different because, as I said in an earlier slide, radiation can be very devastating to the younger and younger child. We know children under age three, if we radiate the whole brain, there's a high risk of what used to be called "mental retardation" or we now refer to as "intellectual disability." I did mention already the tumor biology might be different in this population. We know from recent studies that have been done through COG, and also in Europe, that more of these children have what's called "desmoplastic medulloblastoma," which might be a little bit different.

Let me just take you for a few seconds through what has been done for baby medulloblastomas. It was in the 1980s and '90s that people started taking a chemotherapy-only approach based on the number of drugs. And then in the 1990s, particularly in Germany, people started using the drug Methotrexate. By the 2000s people were starting to incorporate radiation again, but limiting it only to the back part of the brain, not the whole brain, with the thinking that it wouldn't be as damaging to cognition and the child's mental development.

Also in the 21st Century, people have been using high-dose chemotherapy with Methotrexate on either COG studies, sometimes on other studies. People have probably heard about studies called "Head Start III," "Head Start IV."

The role of chemotherapy alone, plus Methotrexate, the role of high-dose chemotherapy like a bone marrow transplant dosing with stem cell rescue, and then chemotherapy with posterior fossa radiation, which is the better is still being defined. We're still refining that. But one thing we do know is that whole brain radiation, whole brain and spine is not the way to go in a baby.

Future treatments are probably going to hinge, too, on the molecular disease stratification. For those people who are now "surfing the net," they're probably aware there's one approach going on through St. Jude, there's a study, SJYC07, where some of the children who have desmoplastic disease as infants are not receiving radiation. That depends on, again, a safe way to do that is probably on an institutional or on some sort of group protocol cooperative group study.

Let's last talk about the adult patient, because this is important. In a third, while we all think about medulloblastoma as a disease of childhood, it's also a disease of young adults. A third of the cases are diagnosed after 15. This is a 24-year-old male, so this could be a college student who comes in with a couple weeks of vomiting, double vision. Likewise, a head CT shows a mass now in the middle of the cerebellum. He too has a good surgeon. He has a gross total resection. Spine MRI is done. There's no evidence of metastasis. And the questions that always come up are, where should this young adult be treated, what treatment should an adult with medulloblastoma receive, and will side effects be the same?

Now, admittedly, I'm someone who practices pediatric oncology and I need to disclose that because I work in a children's hospital I'm biased, but, in general, the pediatric community has a lot more experience treating medulloblastoma than the adult oncology community. Wherever this young man is treated, it needs to be someone who is very familiar with medulloblastoma and the chemotherapy approaches for it.

The treatment that we are going to give, sometimes we try to be the same, but it can be a little bit different. So what are the issues? So there are some issues when it comes to young adults and teenagers with medulloblastoma. The neurocognitive sequelae are a little bit more subtle. They may not have a loss of IQ. They're not likely to wind up being mentally disabled in some way, with intellectual disability, but they still have some issues. Sometimes their attention is off. Sometimes their what's called "psychomotor speed" or "speed of processing" is a little bit slow. Sometimes their executive function is off. Sometimes their organizational ability is a little bit less than other children and young adults their age. These issues may well be permanent.

The other problem in adults is they just don't tolerate chemotherapy as well. Some of the listeners may have experience with a young teenager who has medulloblastoma. When we see the older child and the

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young adult, radiation for those kids can be very hard. Sometimes the radiation with the exposure along the esophagus can make their swallowing and their appetite really blunted. The other thing to point is, and this is going to blend into last segment of the talk, that some of them have what are called "WNT" or WNT tumors, which carry a good prognosis. And we're going to come and talk again about the subtyping in medulloblastoma.

Here's just a very quick preview. You can see here there are three groups, clusters of adult medulloblastoma that used to be called "Group C" -- well, actually used to be called "Group D," in green, or now called "Group 4." There are some that are WNT, in the blue, and there are some that are Sonic Hedgehog, in the red. We're going to talk about what these mean, but here we are.

So the reason these subgroups are important, and, again, this is sort of a coming attraction, I'll explain these groups in a moment, but they have very different outlooks. So three-quarters of adults with medulloblastoma are what are called "Sonic Hedgehog" or "SHH" or "Shh," but we typically say Sonic. And then a small number are WNT, with a very good prognosis, in blue. And then about a quarter are the Group D, or sometimes called "Group 4" now in the year 2014. As you can see, these are to the right here are something called a "Kaplan-Meier Curve." I'm not going to get too detailed, but blue, the ones that are up here are much better survival. So you can see those with WNT and Sonic Hedgehog, people did a little bit better. Those with Group D, much worse in terms of their outcomes.

So we'll just talk briefly about the approach, and then we'll get back to the molecular typing. So for adults with medulloblastoma, many of them are not eligible for cooperative group studies by age, that's a problem, but they often get treated like that. And, again, my bias is that they would be better handled typically in pediatric oncology centers, or at least having pediatric oncology consultation. They get similar radiation.

The hitch comes that when you try to do similar chemotherapy their tolerance is much less. They wind up receiving fewer cycles. Most often we do about eight cycles of chemotherapy. The adult typically tolerates four, five cycles, not a lot more than that. It used to be thought that perhaps their outcome was worse because they got less chemotherapy. That might be a small role, but it's actually probably more -- even when you control for the type of treatment and have the treatment identical, it probably has to do a little bit with the underlying subtype on a molecular basis of medulloblastoma. And here's a good example of that.

This is, again -- a lot of this work here I'm showing I want to give credit where it's due. There have been a number of extremely talented medulloblastoma researchers in Europe, Canada, and the United States, particularly folks -- Stefan Pfister and Marcel Kool in Europe, Michael Taylor in Toronto, and Jae Cho here in Palo Alto, who have looked at this. And we know that a number of these tumors have, again, different outlooks. When we look at WNT in the top panel here -- excuse me, sorry, it jumped ahead there. Just go back. When you look at the WNT tumors -- it has a mind of its own -- I'll just look in the upper left-hand panel. When you look there, you can see that the children who have the WNT tumors do better than the adults with the WNT tumors. When you look at the Sonic Hedgehog, to the right, they're about the same. And then finally when you look all tumors combined, again, in baby, blue at the bottom, kids do better than adults regardless.

Again, this is one of the original papers. This is probably through Michael Taylor, Rich Gilbertson, and others years ago, starting to define the difference subtypes of medulloblastoma. Right now in the current era we have what are called "four molecular subtypes," WNT; Sonic Hedgehog; Group 4, previously called Group D; and Group 3, previously called Group C. Why are they important? We know, looking at this next slide, they occur at different ages, at different genders. I'm not going to get too detailed, but if you look, the panel on the left shows the occurrence by age. Sonic Hedgehog, more common in infants and adults. Group 3 in yellow, more common in older children, six, eight, ten. Group D, or Group 4, can occur at any age. And then the WNT, W-N-T tumors, not as common in the babies, more common, again, in the older child, 10, 12, 15.

Here, infant medulloblastoma, I said at the outset that there's this curious thing that girls do better. Well, it's particularly the younger girls. And we know that girls, Sonic Hedgehog, under the age of three, they

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tend to be very, very good in their outcome and in their survival. And that's why people have started playing around with different trials trying to do less or no radiation of those infants.

I'm going to skip over the next slide. There's some more data on WNT. WNT is a very good behaving tumor. It's probably the best of the bunch. But here's the things that really summarizes everything for you here. This is a slide. You can't go to a brain tumor medulloblastoma meeting these days without seeing this. And, again, this is based on the work of Jae Cho's group. Jae, previously in Boston with Scott Pomeroy, Paul Northcott and Michael Taylor out of Toronto, Marcel Kool, and then also Thompson. So there's a whole bunch here. But medulloblastoma is breaking down into these different groups.

The WNT group, it's about the same, boys and girls, a little bit older child, and adults. Sonic Hedgehog, more common in girls, and a little bit more common in young girls. As we get older, it's, again, adults, about more boys than girls there. And then finally, Group 3, what used to be called "Group C," much more boys. We know this is associated with something called "MYC," M-Y-C. That's an oncogene, and that's commonly seen in Group 3. And then Group 4, again, these are different genes that are called "neuronal" and "glutamatergic genes," tends to do relatively well.

Why does it matter these subtypes? We know that they have different outcomes. If you look down here on the column, which is on the row that says "prognosis," the WNT has a very good prognosis. The Sonic Hedgehog, particularly in infants, is good, intermediate prognosis. Group 3 has a poor prognosis. And Group 4 can be somewhere intermediate as well. So what I'm saying here in a lot of words is we're probably going to move to a system, in the future, where average and high risk are replaced by these groups in some fashion to start moderating what therapy you get. Indeed, we're already starting to see this already.

There's a study being done at several centers throughout the country, SJMB, St. Jude Medulloblastoma Trial 12. This is for some WNT tumors. They will have decreased radiation, only about 1,500 to the brain and spine. The chemotherapy is also markedly reduced. In that same study, for those tumors that are medulloblastoma of the Sonic Hedgehog pathway, they'll also have limited chemotherapy and a tailored or targeted drug called "Vismodegib." It was previously known as "GDC-0449." It's a Genentech drug, and, again, I'm not hawking anything with Genentech. There's a similar compound being developed by the company Novartis. These are drugs that are basically targeting the Sonic Hedgehog pathway.

There's another pilot study, which I don't believe is open just yet, but it's going to be through Hopkins, Boston Children's, and a number of others where there's a plan to do a limited pilot study with no radiation for children with WNT tumors over age three. That's something to be sort of on the horizon.

Let me just close about some of the long-term effects of chemotherapy, and that's really -- why monkey with a therapy that's resulting in 80% cure rates. Well the sad part with medulloblastoma is that many of the survivors are left with long-term sequelae or effects that we hope to avoid. We know that children after medulloblastoma, and the radiation that's necessary, have a risk of stroke about 30 times higher than their sibling or their brother or sister. That's scary, but let me put that in proper terms.

As someone gets into their 40s or 50s, their risk might be one in 5,000 for a general person. 30 times risk would mean 30 out of 5,000. It doesn't mean it's going to happen. It just means the risk is much higher. Endocrine or hormone loss is a big problem. I mentioned growth hormone and thyroid hormone earlier. Hearing loss can be an issue, although, if we watch, probably the best thing to do is prevention, not letting it happen in the first place.

There has been discussion and trials looking at some drugs that are protective against hearing loss. There's been some concern over the years whether that might interfere with the medulloblastoma drug. It doesn't seem to be the case. Neuropsychological damage is really the big one. I'll just sort of put out there that there are a couple points that are important.

Most effects after radiation in terms of cognitive loss are seen particularly starting at about 18 to 24 months after radiation. In the younger children it's more of a problem than in the older child or the adult. In

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the younger child, it can result in loss of IQ. Even in the middle age child it can result in loss of IQ intelligence. In the older child and the adult we might see psychomotor slowing, slowing of getting a task done. They might have problems with short-term memory. They might have problems with organization. Secondary brain tumors, as I mentioned, sometimes people will get another brain tumor or other cancer after the medulloblastoma. It might be because they have a predisposition to cancer through some genetic reason. The other might be that it could be a side effect of their therapy. One of the things we're running into is, as we start to understand a few of the medulloblastoma, not many, that are driven by certain genes, we do worry that are there some kids where we might trigger a second tumor, but that's a very seldom, not a very frequent phenomenon.

Last couple slides here to close on. Now this is some work from one of the investigators here at Stanford, and I'm not showing it because of that, but this was quite a luminary finding now several years ago looking at what goes on in the brain with radiation. And so it's a fancy slide, but basically what it shows, if you look at the panel on the right, here where all the arrows are, you can see what are called "neural precursors" or stem cells that are in normal brain. What happens after radiation, in here you don't see a lot of arrows because those precursor stem cells are lost. We lose a lot of neural cells after radiation because there's an ongoing inflammatory process triggered by radiation. The way to think about it, the radiation produces sort of this chronic inflammatory process. I see that patients in our own clinic, it's like you fell on you knee and skinned your knee and it was inflamed forever, and it can last for many, many years. And that's what was seen.

Last slide to close on. So we certainly need to pay attention to the effects of chemotherapy not only in the short-term, things like hair loss, vomiting, lowering of blood counts, but we also need to worry about long-term kidney and liver problems, second tumors I mentioned, problems in the blood called "myelodysplasia," where cell linings don't come back. We also have to remember, certain drugs are associated with toxicity, Cisplatin with hearing loss; Cytosan or Cyclophosphamide with infertility; and then Methotrexate can cause some problems too in some children; Vincristine neuropathy, I mentioned.

There's a website here. This is a spinoff project through the Children's Oncology Group, [www.survivorshipguidelines.org](http://www.survivorshipguidelines.org). I would really encourage people to look at that site. Melissa Hudson and others have put this together, and it's a fantastic resource looking at the long-term effects of therapy from medulloblastoma and other tumors, so any tumor, not just medulloblastoma.

So I think we've actually tried to stay on schedule here, and I've left you just with a closing thought that medulloblastoma is probably more than one disease that's probably highlighted from an adult, pediatric, and baby classification. We're probably going to see over time some small changes in how we approach the risk stratification. But for the foreseeable future, the backbones of the treatment are going to be surgery, radiation, likely head and spine in most cases, chemotherapy, and there will be increasing manipulations of less radiation and then some targeted therapies to go after some of those genetic signatures we know. So I'm going to stop there because I know questions will certainly come up, and I think we have ample time for that. I really appreciate people's patience as we went through this.

Thank you so much, Dr. Fisher. It was wonderful. If you have a question that you'd like to ask Dr. Fisher, please type and submit it using the question box in the webinar control panel on the right-hand side of your screen. And we have some already. Someone is interested in knowing more about cavernomas as a late effect.

That's a great, great question. So cavernomas are little pooled blood vessels, almost like a blood vessel pooled up. So after radiation, radiation causes changes in blood vessels. So I mentioned during the talk that some people can get a stroke, where the blood vessel gets clogged or sometimes ruptures. A stroke is just a fancy word for lack of blood flow or too much blood, like a hemorrhage, a bleed. So cavernomas are little ballooning. They're not an aneurism, but they're a little bit similar to that, where it's a blood vessel which sort of opens up and will get a little bit large and dark looking. Sometimes there's a little bit of bleeding in it. The good news is that most cavernomas usually come and go over time, and you don't need to do anything. Every now and then and rarely they'll get large and symptomatic. But if it's something you hear about in your child's MRI report, review it with the team, review it with the surgeon,

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most often they don't require any intervention. The only time they get particularly problematic is if they're in the brain stem. That can be a bit of a thorny issue.

Thank you. Someone is wondering about the use of high-dose chemotherapy with stem cell rescue.

It's a great question. So there's a school of thinking -- and Jonathan Finlay at the Children's Los Angeles, and Jonathan's a great physician -- there's been some thinking that a minority of people that using high-dose chemotherapy with stem cell rescue may be an alternative to avoiding radiation, even in children at age six or seven or eight. It's a reasonable thought. It's still unclear whether the survival with that is quite as good and whether the side effects are really less. I think, and, again, trying to be as objective, I'm not a big fan of it, that's a personal, but I think what you're going to see, even between high dose chemotherapy or radiation, as we understand more of the molecular machinery, then we can start to say better who are the children who need a chemotherapy-only approach, maybe a high dose chemotherapy, or who are the children, because of the aggressive nature of their disease, who need radiation. That's probably going to be a middle ground of those two. So I think there may be a role for both.

Interesting. Is it correct to think that a tumor will metastasize or not depending on its molecular structure, not based on how quickly the tumor is detected?

I think that's a great question, and I express this over and over. Again, most tumors that are metastatic, it probably has to do more often than not with the molecular structure. True, you wouldn't want to sit with a medulloblastoma for five years and do nothing, and see what happens. We know it would spread. But, that said, we know that those children who have Group 3 disease have the highest risk of metastasis, and those who are WNT have much lower risk of metastasis, either at presentation or after. And Sonic Hedgehog, a little bit similar to WNT, also not as much metastasis. Group 4, they're sort of in the middle.

The reason this is important, a lot of parents feel guilt-ridden when they come in and their child has metastasis at the word go, is it something they did wrong. And the answer is absolutely not. It's because it's the nature of the tumor. It's not something that was in the control of parents. It's noble for a parent to think that, but it's not realistic.

That's very reassuring. Do you recommend a baseline neuropsych evaluation, and then is there certain intervals that should be done after that?

It's also a great question. And, again, my disclosure, so within the Children's Oncology Group I was one of the people pivotally. There's a study now, if you're onto COG studies, where the children get neuropsychological testing. And so what we sort of came up with was a shortened battery, and the thinking was, yes, whether on a study or off a study, most children would benefit from a baseline and then some follow-up assessment to see where their strings are at present and then what happens thereafter.

On the study on the Children Oncology Group, neurocognitive study that all the medulloblastoma children are now tested on, they get tested -- the baseline, we typically do at about six months after diagnosis, plus or minus three, then we do it again at years two-and-a-half and five. But I would say to you, at the very least, even if a child doesn't get a baseline testing, getting some follow up two or three years after diagnosis is important. It can be done out in the community by a community neuropsychologist. That can be costly.

And it's important that parents understand their rights to have it done through the school. If they have concerns about their child's performance, it's within their right in any state in the 50 states to tell the school they want their child assessed. It's through a process called "IEP," appointed for parents. I'm a big fan of schools. I love schools, but when it comes to IEPs and a request for that, it must be by law in writing, and not just by word of mouth at the parking lot or the water fountain. If you want to get that kind of thing done through the school, a simple note saying, "I have a concern about my child's cognition after medulloblastoma and I want them tested," that will get a result in a psychological or psychoeducational assessment in the school.

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And sometimes it can be really difficult dealing with those schools, so it's nice for you to mention to parents how they can advocate for their children. There's a follow-up question about the neuropsych testing, wondering if you'd recommend neuropsych testing for an infant who had chemo only, or is it a radiation-related issue?

That's a great question, and just tying back to the school. And, again, I do think schools are great things, and the teachers do great work. They're simply overwhelmed. And I think your point is you do need to be persistent. I always say to our parents, the polite squeaky wheel gets the grease.

So what about an infant who received chemotherapy only, do they need testing? And I think the answer is probably, yes. And what is the reason? There have been a number of studies now over the last ten years showing that even a child who gets a tumor in the back part of the brain, cerebellar astrocytoma or pilocytic astrocytoma of the brain, that even those children who get surgery only, no radiation, no chemotherapy, that they have a number of psychological effects, certainly nowhere near as severe as medulloblastoma and radiation.

But the idea that chemotherapy causes no problems is probably a little bit too optimistic. I don't think it causes major problems. But the combination of having the tumor, sometimes hydrocephalus, and then also having had surgery, sometimes an infection or a shunt, and then even in chemotherapy-only, those are all things that can weigh into some effect on thinking and school performance. And I think we tend to lean toward doing something than not doing something. Sometimes there's this tendency in the school or the parents think, "Oh, everything is going to be okay because my child didn't get radiation," and hopefully that will be the case. But it's much better to understand is there a problem, because if there are there are a number of strategies to implement at the school to try to optimize the child's performance. You know, a theme we always like to say in clinics, we want the children to be cured of their medulloblastoma, but we also want them to be successful.

Of course. Someone's asking about the best practice suggestions when monitoring a child in the off-therapy phase of care.

Right. So that's a great question. So there's been some work looking at this. What's the best way to follow up a child when they're off therapy? A former – not a former – a colleague and former fellow, Dan Bowers at Southwestern in Dallas did a study of this a couple years ago, looking at how are children after their brain tumor, where and how are they followed; sometimes in a medical oncology clinic, pediatric oncology, sometimes a specialized late effects or health after therapy clinic. There are all sorts of ways they could be followed.

I think it's two ways to follow the child. One, they need to be followed by someone who understands the long-term effects of chemotherapy and radiation. Sometimes that's the neurologist or neuro-oncologist. Or sometimes it's a specialized long-term or late effects clinic in the oncology center. That's often better in a pediatric oncology center than adult. Medical oncologists are wonderful people, but they don't understand a lot about the long-term effects.

The other thing, I would very much encourage ownership in both the parent and the child, looking at the Survivorship Guidelines, that was the website earlier. There's nothing there that's scary. It's very much like a Wikipedia of a lot of stuff, but it's very, very handy to know. It is sort of standard to do something at least once a year, even six, seven, eight, ten years out. Follow up probably goes on lifelong. That all said, we do know a number of children, particularly as young adults, don't want to come back to clinic. They want this out of their life, even when things are going okay. But there can be issues that come up with reproduction, fertility, heart function, lung function, memory, and liver. And we want to make sure the kids are healthy and we want to -- again, prevention much easier than intervention.

Perfect. Wondering if proton beam radiation has the same effects neurocognitively as regular radiation

So, a good question. So proton beam radiotherapy probably will have an increasing role in the future in brain tumors. But the idea of proton beam radiotherapy, in essence, is when the beam goes in there's

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less exit dose. When it comes to the whole brain radiation in medulloblastoma, since the whole brain is being radiated, it may not be as big an issue. Where it does come up in medulloblastoma, particularly is that when you're radiating along the spine there's less exit dose there, much less problems of radiation along the esophagus, less problems with appetite and things like that.

In terms of its effectiveness, probably is as effective. There's no data that suggests it's any less effective. I think it's as effective. I don't think there's any question about that. In terms of will it be cognitively sparing, in those tumors that are getting focal radiation or just part of the brain radiated, there probably is some advantage. We're still learning, and there's some good work that's coming out of Boston and Nancy Tarbell and Torunn Yock's group. But in terms of how much of an advantage, we don't know. In medulloblastoma, probably not a big cognitive advantage. Maybe a little bit, but probably not a lot.

Okay. We have a couple more. We have a few more minutes. Someone's wondering about the average timeframes for recurrence and the treatment if there is a recurrence. Is there an average timeframe?

There is. So, things that we know today, we know that babies, when they recur, they seem to recur a little bit faster. We know historically infants, when they recur, they tend to recur about six or so months after their diagnosis on average, can be longer or shorter. And then for the older child, recurrence is very often about 15 or 18 months after the diagnosis, once the therapy is over. It should be clear, it's not because the therapy was stopped, it's just this is when recurrence occurs. Remember, the therapy takes place over about 12 months. So it is why we keep doing MRIs and watching very closely.

Medulloblastoma, we know that our best swing of the bat is always the first swing. The second swing is not as powerful, not as effective as we like. When we do that, we encourage people to look at different cooperative group studies, both through the COG and Pediatric Brain Tumor Consortium. If they don't go on the study, we also consider things like multiple chemotherapies. Sometimes we'll try to give more radiation, that can be hard. Sometimes people will talk about high-dose chemotherapy and stem cell. No one of them has been shown to be superior than the other.

Good to know. Wondering if there's any chance that what has been learned from -- I'm going to say it wrong, sorry -- genomics will help treat or heal some of the late effects that some of these patients have experienced from the radiation or the chemotherapy?

That's a great question. As we know these genetic signatures or this classification, will that lead to better outcomes, either prevention or intervention? It will lead to better outcomes on the prevention side because we have certain tumors like the WNT, and possibly Sonic Hedgehog in the little kids, the infants, where we might be able to give less radiation or no radiation. So that's very exciting.

The genomics might not help as what do you do once you know there is damage or you have to give therapies that are known to be damaging. But, still, there's going to be a role for genetic or genomics-like work looking at things to prevent that neuro-inflammation. People have talked about a number of ways on a molecular or genetic level to try to blunt or sort of smack down that neuro-inflammation. We don't know what the ideal drug is yet to do that, but there will probably be some tests of that coming up in the next years ahead, looking at ways to sort of moderate or minimize sort of this chronic brain inflammatory process that goes on with those kids that still require radiation regardless.

Thank you. Once the child reaches adulthood, who should they be followed by? There's always that problem when you transition from pediatrics to adult. Should it be an oncologist, a neurosurgeon, a neurologist, how do you know?

Great question. And so ideally would be if they could stay in the pediatric oncology clinic as long as possible. Some places will let the kids stay there until age 24. In our institution we'll let them stay until 30. But every place has a different practice. They probably would benefit, many of them, from either an oncologist and/or a neurologist. The neurologist will be more sensitive to the hearing and the neuropathy, and sometimes the learning issues. The oncologist will know more about the drugs. Unfortunately, neurosurgeons -- I love neurosurgeons, but they don't know a lot about the long-term effects, and they

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may not be the type of doctor who has the most time, because of their big demands, to explain some of the side effects of long-term effects of the drugs.

Okay. Another question, “Is there any risk for the return of the disease when they’re taking the growth hormones?”

That’s a great question. People have looked over the years. There was a very nice study in the Journal of Clinical Endocrinology and Metabolism, now, years ago. And there does not appear to be any increase of recurrence by using growth hormone. That said, most endocrinologists are still a little bit skittish about this when the idea of growth hormone comes up. Most places want the child to be at least 12 or 24 months out from therapy before they’ll start growth hormone. We try to push toward 12 months, because time is growth. We want to have more growth than less, and we want the children to be as normalized. So the data say that it’s safe, and 12 months out would be safe to do it. Still, some endocrinology hormone docs would like to wait 24 months. But it does appear to be safe, and there does not appear to be any increased risk of recurrence by using growth hormone.

All right, I’m going to sneak in one last question because she’s been so patient with us. Someone’s wondering how they know which group they fit into. She said that she’s desmoplastic, no spread, clean CSF, wondering if she’s in the WNT group, the Hedgehog group, how do you know?

That’s a great question. It’s a great question to close on because it’s going to be a stay-tuned question. So those molecular classifications, they’re not done in routine laboratories or commercial or what are called “CLIA-approved” labs. It’s not something where you can go to a hospital in Miami, New York, whatever, and say, “Send it to the lab,” just like you do for a sugar or for a sodium. And so right now there’s still none of the research level. That said, we know that someone who is desmoplastic, no spread, often a girl, those tend to be Sonic Hedgehog group, and so that’s probably where that person is.

But right now we’re not ready for primetime yet, because we’re getting close but we’re not at the point where we can turn around molecular classification fast enough to make decisions and with 100% certainty enough to make decisions. For instance, we’ve learned that within the Sonic Hedgehog there are some that are very good Sonic Hedgehog and there are some that are a little bit more aggressive where they have a double-whammy of Sonic Hedgehog and MYC. So we need to be careful before we sort of run and make a whole generation of decisions based on the molecular classification. And that’s where the research teams now are sort of working, trying to figure out if we go ahead and embark on trials over the next several years using molecular classification, what’s the best system we can use so we hopefully don’t place any children in the cracks or anyone at risk.

So right now it’s still in a research basis. It’s not fully ready for primetime. Right now, we’re still using that histologic, as this person mentioned, classic, desmoplastic, anaplastic. But that said, we know that anaplastics probably most often go with things like Group 3, the desmoplastics vey often go with Sonic Hedgehog.

Wonderful. Sounds like we’re going to have to schedule a Medulloblastoma Part 2 in the future when we have some results. That’s all the time that we have. And, again, I want to thank you, Dr. Fisher. I want to encourage anyone, if they didn’t get their questions answered to call us on our care line. We also have a medulloblastoma brochure that we would be happy to mail out to you. You can call our care line at 800-886-2282. So let’s pause for a moment to conclude our webinar recording.