GILLES ATLAN >> thank you for joining for this webinar; for the captioning, as you can see on the slide, you have to click on the button “cc”, and then you will see the live captioning.

Thank you for joining this webinar. My name is Gil. Before we start the discussion, I would like to say a few words about NF2 BioSolutions.
So my daughter is 15 years old, and she has NF2. Because of her, four years ago, I joined with several families touched by NF2, and together we launched NF2 BioSolutions non-profit.
Our main goal is to focus on funding and research for long term treatment of nf2. As you know, unfortunately today, the treatments are often short term and risky. So thanks to your donations, the donations to NF2 BioSolutions, we are today funding ten labs that are working on therapies, and please consider donating to NF2 BioSolutions so we can get closer to a long term therapy for NF2.
The 29th of November is Giving Tuesday, and we will be running a big fund-raiser online. As you know, in the meantime, until we have a good treatment, we need to do surgeries, radiation, cancer drugs, or simply wait and see. Unfortunately, the tumors are not waiting.
That's why, in addition to funding research labs, we run webinars so our NF2 community can better be informed and take better decisions. Today this is the webinar number 9. You can watch all the other webinars on our website or on the “I Need a Cure” YouTube channel.

So let's start with this important webinar and giving the mic to Mary. Thank you very much.

MARY SELL >> Thank you, Gilles.
I'm Mary Sell, a parent, and I also have a 15-year-old daughter with NF2. I'm currently serving as director for NF2 BioSolutions, on the board of directors, and I'm also the Iowa ambassador.
I got involved with NF2 BioSolutions not too long after my daughter was diagnosed because the people involved with this organization, including Gilles and Nicole Henwood, give me so much hope that better treatment options and even a cure will be found for NF2.
I have the honor of introducing our incredible panel of experts today, who are here to share their knowledge and time with us.

We have Professor Shannon Macdonald, who is an associate professor of radiation oncology at Harvard Medical School. She's an Associate Radiation Oncologist at Massachusetts General Hospital. Dr. Macdonald is credentialed at Boston Children’s Hospital and the Dana Farber Cancer Institute. She's a primary investigator for the Children’s Oncology group study ACNS 2021, which is also open for young adults through the adult cooperative group. She's a specialist in Proton Therapy and is a Pediatric Radiation Oncologist and Dr. Macdonald is the chief of base of skull and sarcoma radiation services at mass general hospital.

I'd also like to introduce Professor Michel Kalamarides, who's the head of the NF2 Center at the hospital in Paris, France. Dr. Kalamarides is a neurosurgeon at the service of neurosurgery, also at the same hospital. He's a professor at Sorbonne University in Paris, and Dr. Kalamarides is an adjunct professor of head and neck surgery and an adjunct professor of neurosurgery at UCLA.

I'd also like to introduce Professor L. Dade Lunsford. Dr. Lunsford is a Lars Leksell distinguished professor. He's a neurosurgeon at the department of surgery and radiation oncology at the University of Pittsburgh. Dr. Lunsford is the director of the University of Pittsburgh Medical Center for image-guided neurosurgery. He's an associate resident director and chair at UPMC on the technology and innovative practice committee.

So, again, thank you to the three of you for being here today to share your knowledge and time with us. We're going to start first with an introduction to some of the different kinds of radiotherapy. So Dr. Lunsford and Professor Macdonald are going to give us a brief introduction, and after the introduction of different kinds of radiotherapy, we'll get into the panel discussion with questions from our audience. So we'll go ahead and turn it over to you, Professor Lunsford.

PROF. LUNSFORD >> Thank you. We'll see if we can get all of the technology to work well. Can you see this slide? And we go to full screen there?

MARY SELL >> Yes, we see full screen.

PROF. LUNSFORD >> I'm going to go through a few slides back here just to clarify some terminology, and thank you for allowing me to participate in this session.
One of the things to first understand is a difference in using wider field radiation therapy. Using multiple sessions versus using a very focused technique that can be efficiently delivered in a single procedure, a term that is called radiosurgery as opposed to radiation therapy.
And the reason it's called this is because of its use for precision guiding devices to be able to facilitate treatment focused on individual tumors in a single treatment.
This sort of upset an apple cart of about 75 years of knowledge when it was first proposed, because it changed the concepts of understanding how tissues respond differently compared to when this is done in a single treatment versus in a multi-session type of treatment. Really the term was first created 70 years ago by Lars Leksell working at the Carol Institute.
To do this, a guiding device is used, which is where the term “stereotactic” comes from. It's a three-dimensional way to be able to deliver the radiation. And across the world, there are a variety of techniques where this can be used.
Certain modified linear accelerators, gamma knife, zap knife, all of these represent technologies from different manufacturers that allow this type of treatment to be done.
Our work over the last 40 years has been related to the use of gamma knife, and worldwide there's a huge experience with this, with more than 10,000 publications related to its outcomes.
As it applies to patients with NF2, this includes many patients with various cranial nerve schwannomas, especially the 8th nerve, but also facial nerve trigeminal nerves and lower cranial nerves, and certain gliomas and certain ependymomas. Many of these are done after initial surgical approach are done.
It's very convenient for patients. It sort of has a surgical bias based on the guiding device, and it's typically done in a wheels in to wheels out approach.

So we started looking at this not only from its potential role in this difficult disorder, but not only its outcome role, but also what it does in terms of preserving the neurological function, the cranial nerve function, as well as looking at risks.

Typically the way this is done, a patient with mild sedation has this guiding device applied to the head and make a new MRI scan to define the target, and we develop a plan which allows us to treat the tumors in a single treatment. There's no opening of the skull. There's no incisions.

It's paramount that the effectiveness is confined to the tumor with very sharp falloff of the delivery of the dose outside of the target. And more recently this device has been updated to in certain cases to allow this to be done with a more mask type of mobilization, which works in certain patients, especially in patients who are not claustrophobic or patients who are somewhat older. Typically, the goal of this is to inactivate growth of the tumor and monitor the cranial nerve function afterwards and to see, hopefully over the course of time, gradual regression or shrinkage of the tumor and a low risk of side effects.

We recently completed a study through a multicenter consortium that we organized here in Pittsburgh. There are now 32 centers that participate in this, and we looked at 267 NF2 patients in this group. There were 328 tumors, so many of these were bilateral, or both-sided, tumors. These patients were typically in the younger age group, and the goal is to give a single dose in the margin of the tumor, minimum dose of 12 grams.

What we found over time is tumors can be arrested in growth of 77% when we look at outcomes of ten years. But 11% of the patients required repeat procedures, usually for new tumor development or delayed tumor progression of a tumor. What we found out is that in general younger patients and those with one-sided tumors do better and respond to a little higher dose than a single treatment.

But the number one goal of this is to look at how the patients' outcomes are maintained, and when we looked at patients, especially with these hearing tumors, that at five years we can maintain serviceable hearing in almost two-thirds, but ten years that hearing preservation rate has dropped to about one out of three.

For those patients, because the facial nerve is very close to these tumors, the goal was to preserve function of the facial nerve, which can be done in the vast majority of patients with rate 1, rate 2 function on long-term outcomes. One of the concerns for the delivery of radiation has always been what is the subsequent risk of other tumor development? or what is the risk of conversion of a tumor which is histologically benign, a tumor that is more aggressive or malignant?

There have been sporadic cases reported along with this often in the literature, but sometimes this gets carried through social media as a definitive answer. At present rate we find no convincing evidence for increased risk after single fraction radiosurgery, which comes from an article we published in Lancet Oncology a few years ago, which the risk is similar to the risk of a general population who have a primary CNS tumor but do not have NF2.

In this long term follow up that we looked at, where 75% of the patients had freedom from any additional treatment by 15 years. Radiation related tumor development or radiation related malignant transformation of a treated tumor were not seen. We would just add, in addition to those tumors of cranial nerves, tumors involving – or meningiomas involving structures of the brain, which is a very common part of NF2, can also be treated effectively by this same type of technique with very high nerve preservation rates in terms of vision and feeling of the face.

So just to summarize our philosophy related to this, we understand, as do patients and families over time, that this is a very complex genetic disorder. The impact varies with individual patients. The decision makes as to what to do in terms of management or when to do something has to be balanced very carefully between the overall risk and benefit. So when tumors are symptomatic and shown to grow over time by imaging, both surgery and radiation options need to be considered, and we must balance that with the outcomes of this, and the patient's life and goal is also the preservation of neurological function.
It may be over the course of time need to be repeated because of the risk these tumors will grow or new meningiomas will develop over time, and each time that problem presents clinically, it must again be reassessed as to which option may be the best with those patients. Thank you.

MARY SELL >> Thank you, Professor Lunsford. Next we'll hear from Professor Macdonald. If you would like to share a little bit of background on proton beam therapy, we'd like to hear a little bit about that next.

PROF. MACDONALD >> can you hear me okay and see my slides?

MARY SELL>> Yes.

PROF. MACDONALD >> Great. Thanks for the opportunity to speak with you today. I'm going to go over some basics of radiation therapy with our focus on proton therapy and some examples and comparisons of proton radiation versus standard x-ray with a focus on proton radiation.
I know we have a lot of families in the audience, I thought I would go over the basics of radiation therapy to start, how it works and how we can better deliver radiation.
There are types of proton radiation treatments, along with some basics of proton therapy. As a background, radiation therapy is not familiar to many people who are not radiation oncologists or radiologists. There are many different forms of radiation. The types of radiation that we'll speak about today include x-rays, scanners, and proton therapy. These are types of radiation that are beneficial to meningiomas and tumors, but it can also be helpful to normal, healthy tissue.
When you're delivering radiation therapy therapeutically, we're always trying to give the highest dose we can and the therapeutic dose needed to the tumor, but minimize any radiation therapy to healthy tissues that are not involved with the tumor. Protons are x-rays. They need to enter and exit the body; similar to gamma knife as a form of x-ray therapy, proton therapy is similar in that's produced by an accelerator or machine.
Protons work by damaging DNA in cells, and cancer cells are more susceptible than normal healthy tissue or normal organs are to radiation therapy, but it is a form of therapy that damages the DNA in cells, more so cancer cells than healthy tissues, and causes them to die or lose the ability to replicate.
Because of the healthy tissue versus tumor, most radiation sessions are given over a fraction of course, where there are many treatments over the course of weeks, five or six weeks. But some radiation sessions are delivered in one treatment, such as gamma knife treatments, and this is because of the ability to focus a very high dose in a small, small area while minimizing any high dose to the surrounding area. For radiation therapy, often you'll have an immobilization device that keeps patients in a firm position every day.

Sometimes this is in the form of a mold that is soft when you lie down on it and conforms to the body. Sometimes it's in the form of a mask. We have some very rigid masks, but this is a softer mask with a mesh material that goes on and hardens to the shape of your face.
There are many terms for different types of radiation therapy. Commonly used types of radiation therapy today are conformal radiation therapy, which is delivered with a machine in the accelerator. Intensity modulated radiation therapy, which is delivered with an accelerator but in a more sophisticated way. Another term is volumetric part therapy. And then there's stereotactic radiotherapy, which is delivered in a more rigid frame and a smaller number of treatments, sometimes one, sometimes a few treatments.
And then there's proton radiation, which differs by being a particle that enters the body and stops. Unlike X-rays, proton therapy does not have to go through the body, continue to go through, but will stop.
For radiation, whatever part of the body we're treating, we typically use a CAT scan and an MRI, and we have machines that can do both, and we work with our radiologists to bring in any images that have been obtained, and that would be an MRI, a CT, a PET scan, any type of imaging that can be brought in and used to whatever you get in the treatment position. Tumors are delineated based on MRI and CT, and often a margin for safety instead of error.
Linear accelerators, again, are machines that deliver proton radiation, which produced lethal electricity, where electrons find a target and create protons that can come out of this machine. There are blocks in the machine that block the healthy tissue from seeing radiation, and the radiation comes through in this open area. A lot of patients ask: Do I need to wear an apron or something on my body? But the blocks are much thicker than anything we would put on the body and are in the heart of the machine.

IMRT treats with tiny little micro beams, and it's a very sophisticated type of photon therapy. Then stereotactic treatments are typically delivered with many, many tiny beams, which end up delivering a very low dose outside of the target area and a high dose to the target area and the different types of therapy include gamma knife, stereotactic radiosurgery.
This is an example of a gamma knife machine, one of the most stable types of treatment. Because of this, this is a machine that has 201 sources that deliver a very high dose to a small target. And other low dose anywhere outside of that target. This is generally done in one day.
This is a rigid frame with a bite lock that is used for stereotactic radiosurgery delivered with Linac. Which is similar, delivers very small beams for a tumor that spreads out on a very low dose.
Photon therapy is special in that it is not a form of proton therapy. It is a totally different type of treatment, and it is a particle therapy. The other type of particle therapy that you may hear about is called photon proton beam therapy that is not yet available in the U.S.
It's a much more common type of particle therapy. There were only three machines in the U.S. in 2006. There are now about 40. So it's becoming a more widely available form of therapy.

And photons in a proton beam enter at a very low dose can treat any depth up to 32 centimeters. When you determine how deep you want the beam to go by determining the energy of the beam and how fast it will travel. Then it delivers its dose over a very small area and delivers no dose after it treats the area needed. So the major benefits comes from low exit dose, but there are also benefits for some treatments for less entrance dose as well.

Again, there's been huge growth since the early years of proton therapy with 40 proton centers in the U.S. and many more under construction.

This is an example of our proton unit. We have a cyclotron, which accelerates protons to about two-thirds the speed of light. They are then fed out through a beam line, which is a series of very powerful magnets and degraders. The cyclotron is one form of machine that produces protons.

The other form is a synchrotron. It creates the highest energy protons and degrade it. You don't need the highest energy on the more superficial target. We have three treatment wings, and a separate synchrotron machine. So a total of four rooms for proton therapy.

Protons are pulled off of water, essentially and accelerated in the cyclotron. This shows you the beam line. They are then delivered to one room at a time.

This is a gantry room, which is the most commonly used room. We have two gantry rooms and a fixed scheme. A fixed scheme can be used to treat targets in a sitting position or move patients around the beam.

The gantry, besides the job of moving the beam around the patient, is a three-story unit, which is a very large machine compared to a linear accelerator, and weighs about 100 tons. So this is a massive piece of machine despite the fact that it's really just made to move protons around a patient. The fixed room has a simple, very sharp beam, and is often used to treat eye tumors, sometimes small groin tumors. And this again is just an example of the cyclotron and the gantry beam.

So for proton therapy in the past, we've had to select very carefully the patients that we were treating. We still do select tumors that are likely to be more amenable to proton therapy and the benefits. We select patients with tumors in often very young patients, and young adult patients.

Patients with NF2 typically have very curable tumors, and we're trying to reduce side effects. Treating with protons benefit using radiation therapy. These are the tumors that are optimum and our efforts to decrease late effects for these patients. For the tumors we're treating for NF2 patients, we're usually not trying to prevent the cure rate, but trying to reduce the late effects.

We are showing the effects of a retinoblastoma, which is not a tumor. But with proton therapy, and this is from 1995, there are many in the interim. But I show p proton plan from 2012, you can see the lessening of effects from radiation, and these are children that have a very, very high risk of forming a second malignancy, so it was a very good population to look at ten-year outcomes and see a difference in the rate of second malignancies, which we did for proton therapy.

The rate with proton therapy was 14%. This was a study that MGH did in conjunction with Boston Children’s Hospital for this rare tumor that is prone to second malignancies and forming them early, to show that there's a benefit to decreasing the series because of increased tissue.

This is an example of spinal treatment. The photon continues to exit the body. But here the bone is being included. If you include the spinal canal, you have a vertebral body risk, like esophagus, heart, lungs, arteries, GI system. So this is a major area of benefits of spinal ependymomas.

This is an example of treatment of a brain ependymoma, and this is showing the evolution from photon to proton, and then finally something called IMPT, which is available in almost all proton centers today. So many excellent photon and proton radiation techniques exist for the treatment of these tumors and for the tumors associated with nf2. Thank you very much for your time.

MARY SELL >> Thank you, Professor Macdonald. Next we will go ahead and just start going through questions that our audience has submitted. So we're going to do a panel discussion now with the three of you. Our audience can continue to type questions in the question section of the meeting as well.
So we're going to talk about applications, protocol, and limitations of radiotherapy to start.

I'll direct this one to you, Dr. Lunsford. I know you've addressed some of these in your slides already, but what is the strategy for radio surgical treatment of bilateral Vestibular Schwannomas?

PROF. LUNSFORD >> First of all, we do not treat two tumors at the same time with radiosurgery, and in general the decision-making relative to tumor selection, patient selection comes down to size of the tumor, progression of the tumor over the course of time, usually by imaging studies done over multiple months or years, and finally the overall status of the patient's hearing.
So the goal really is to inactivate or prevent further growth of a tumor which is known to be growing.
There is no absolute way to predict which tumor in NF2 will grow when or how fast. So as a general rule, we're going to select patients who have symptomatic progression, that is, a tumor that has been growing over the course of imaging, which may be months or years, and who is getting new neurologic problems specifically hearing.

MARY SELL >> Okay. And for you, Professor Kalamarides, in your experience with patients in the clinic, when are you recommending or not recommending radiation for Vestibular Schwannomas?

PROF. KALAMARIDES >> Thank you. We have a gamma knife in our department, and we have a proton facility in France. I think what Professor Lunsford said is very clear. We recommend regular surgery when we see accelerated tumor growth.
I'm not in favor of treatment sometimes performed in some centers, and this is a big question about the timing of gamma knife or surgery. Probably gamma knife or surgery is exactly the same. It's different in terms of maybe time in recovery, but it's exactly the same discussion.
But I think I'm managing the reference, and we have to explore all the options. So for me, when I see an NF2 patient with bilateral vestibular schwannomas that are growing similarly, I think that a treatment is not reduction. I would recommend to the patient options like bevacizumab or other treatments.
What I understand from the presentation from Dr. Lunsford is that, in fact, it seems the gamma knife is working better for the smallest tumor which is normal and in the older patients, right? So I think that we use gamma knife mostly for older NF2 patients with a small growing vestibular schwannoma. In very young patients we don't use the gamma knife.
The radiotherapists don't want to use the gamma knife. They prefer to use the proton beam therapy. And to finish, there is a risk of maybe with a young patient. We'll discuss this later.
So I think for bilateral in the case of tumor growth, I prefer to use systemic treatment.

MARY SELL >> Thank you. Dr. Lunsford, maybe you can address this question. What is the latest data on the impact of radiation on vestibular schwannoma – the impact on hearing, facial nerve function, and balance?

PROF. LUNSFORD >> So I presented a little of this in my talk. What we've seen is tumor control long term can be achieved in about 75%, that is, three-quarters of patients. We can preserve hearing early in the post-treatment phase, very high level in probably 75% of patients.
But by the time ten years pass, then only about one-third of the patients have hearing at a level which can be saved, for example, used on a cell phone to communicate with that ear.
The natural history of these tumors is over time to grow, but the rate at which they grow is one of the issues that we try to look at very carefully. But once a patient has evidence of growth and hearing getting worse, in my view, that's the time to consider radiosurgery because we can save hearing when the tumors are smaller, we can save hearing when the hearing is already at a high level. Much better than we can save hearing in a patient whose hearing has already begun to deteriorate significantly.
Certainly treatment does not restore hearing. So treatment can't bring hearing that's already deteriorated back. That doesn't happen.
As you know, there are also options for surgical removal of these tumors, and sometimes partial surgical removal can be considered. Then in certain patients, if hearing is still preserved at that point, we might add radiosurgery after partial resection of the tumor.
I will say that I think there's one tumor which I think very clearly should be treated primarily by radiosurgery, and that is nf2 patients with facial nerve sheath tumors because those patients have the best chance of facial nerve function preservation as opposed to surgical removal of those tumors. So we prefer to use gamma knife early in that group of patients to have the best chance of long term facial nerve function. That includes the patients who have vestibular or acoustic neuromas because the cause of weakness to the face is much less than patients whose tumors are smaller who are treated sooner.

MARY SELL >> For Dr. Macdonald, is radiation used for meningiomas? And what about optical nerve meningiomas?

PROF. MACDONALD >> Yes, radiation can be used for that indication, and that's actually, I think, a great indication for proton radiation because of better sparing of the pituitary gland, the adjacent brain, and also bony areas. If it's a child and they're growing, it can preserve vision, if there's still vision remaining. But because the doses we need to use are tolerated by the optic nerve. And it can decrease the dose to the retina which can be high enough to cause some vision loss. So I think it's a good indication for selective patients, and proton radiation would be a good indication for that.

MARY SELL >> A question for all three of you or any of you, is radiation used for spinal ependymomas?

PROF. MACDONALD >> Yes.

PROF. LUNSFORD >> I'll start. Yes, the answer is yes. For symptomatic tumors that are growing, yes. Radiation typically done in fractionated technique is used. But there are forms of spinal radiosurgery that can be considered in certain patients as well so that the number of sessions is reduced compared to the more standard fractionation for these types of tumors.

PROF. KALAMARIDES >> Just the point, I think there is no place for radiotherapy for spinal ependymomas in NF2 patients because I think that most of symptomatic are cystic, and I don't think that radiation is a good option for this very low grade ependymomas.
I've never seen any indication in NF2, any experience on ependymomas. Do you know any series of patients treated by radiotherapy or proton therapy for spinal ependymomas? I don't think there are.
I think that observation, surgery, bevacizumab for the cystic part is very large, for surgery, but radiotherapy, I'm not sure.

PROF LUNDSFORD>> what do you do for a recurrent tumor after initial surgery?

PROF. KALAMARIDES >> in fact, it's very strange because we observe, in fact, meningiomas are rare. The rate of reoccurrence after surgery is low, sporadic. It's the same for NF2 related ependymomas. So it's a rare option to do recurrent surgery. So recurrent radiotherapy -- you know radiotherapy and surgery are exactly the same. It's an indication of tumor growth. It's rare to see recurrence.

I have just a question for you, Dr. Lunsford. What is your impression about the results - I know the response, but just on the patients, the results of radiosurgery for NF2 vestibular schwannomas compared to sporadic?
Because sometimes with surgery it's more difficult to remove a vestibular schwannoma because in the patient sometimes they are collision tumors. The results of surgery is not so good for sporadic. I think it's the same for an NF2 patient. What is your experience?

PROF. LUNSFORD >> I agree completely, yes. If we compare patients with sporadic unilateral vestibular schwannomas, hearing preservation rates, facial nerve preservation rates are much higher, especially because these are being diagnosed sooner now, and tumors are often smaller than they used to be than in prior years when they were diagnosed.

PROF. KALAMARIDES >> to me, the question for you is you don't think it's something more based on Vestibular? -- because we know there are multiple tumors, in fact, in NF2, looking like one big tumor but are small. So maybe I think it's maybe more based on biology or anatomy or maybe more than that.

PROF. LUNSFORD >> certainly I agree. Unilateral tumors can displace cranial nerves. NF2 related Schwannomas engulf or swallow the nerves, in which case either surgical or radiosurgical options have much higher risk of those nerves getting worse afterwards.

PROF. KALAMARIDES >> and we know that in young NF2 patients with fast growing vestibular schwannomas, medical treatment are not working, and I know that surgery sometimes has to be done, and radiosurgery is one of the most difficult cases to be treated. Young NF2 patients with fast growing schwannomas, they are from the beginning medium sized or large. It's the same for surgery and radiosurgery, I think. It's the most difficult cases.

PROF. LUNSFORD >> I agree. In younger patients.

MARY SELL >> Thank you. We're going to ask for a little audience participation now, and we'll have Gilles launch a poll. So go ahead, Gilles, please launch that. Audience, you can answer the question that you see on your screen.

What type of operations or treatments have you done? You can checkmark multiple answers.

Second question there, do you have a planned intervention in the near future?

And as a panelist, I cannot see those results. Can you see those, Gilles?

GILLES ATLAN >> yes, I think when I end the poll, it will be displayed. But let's give another five seconds for people to answer because I still see some answers coming in.

MARY SELL >> okay.

GILLES ATLAN >> so let's finish with this poll. Share results.

MARY SELL >> Thank you to our audience for participating in that poll. We're going to move on to a few more questions about combining radiotherapy with other types of therapy.
So for Dr. Kalamarides, we used to believe that radiation made subsequent traditional surgery more difficult. Is that still the case?

PROF. KALAMARIDES >> I'm not sure it's the case especially after gamma knife. I'm doing some surgery for vestibular schwannoma in sporadic. I don't think there is a difference. When you decide to do surgery or a case of gamma knife, which is rare, you deal with a large tumor, but technically it's no different.
I don't know the experience of Dr. Lunsford.

PROF. LUNSFORD >> I think there's a fair amount of disinformation out there that patients have received that surgical removal after radiation or radiation therapy has become more difficult. I think in some cases it may be even less difficult because one of the effects is to change blood vessel supply of these tumors.

But in terms of --

PROF. KALAMARIDES >> excuse me, it adds some difficulty after classical radiotherapy, you know, 55 Grays. So when you have to do surgery, it can be more difficult. But after gamma knife, no. There is honestly no difference.

PROF. LUNSFORD >> that's our experience as well.

MARY SELL >> and another question. What about the combination of radiation and Avastin or other drugs? Is Avastin needed or useful to reduce inflammation triggered by the radiation?

PROF. LUNSFORD >> I can start with one answer. We use Avastin frequently when we detect reaction or edema is swelling around the tumor, which does not necessarily respond to a short course of cortisone anti-inflammatory agents or steroids. We then move to using Avastin in those patients.
I don't think it changes the response necessarily of the tumor or improves tumor control, but it's very effective when dealing with radiation related complications of tumors.

PROF. MACDONALD>> the same. We also use it after with swelling due to radiation.

MARY SELL >> I'll start with you on this one, professor Macdonald. What medical centers have performed the most procedures with each type of radiation on patients with NF2?

PROF. MACDONALD >> I'd say that's a difficult one to answer. For proton radiation, we've had protons in some form since the 1960s, so we have a lot of experience with protons. But we don't have a gamma knife unit. There are several gamma knife units in the U.S. and abroad, so I can't answer for the world, but that's another very commonly used modality. And the stereotactic treatment is widely available as well.

PROF. LUNSFORD >> I think as a general concept for patients and families, if you can find centers that have a team approach with people who are involved in all the modalities that includes a neuro oncologist who may be involved in using bevacizumab or Avastin, radiation oncologists, neurosurgeons, so that all the options can be properly evaluated in individual patients, including the timing and the various roles.
And one of the ways that patients can look at that trying to define a center of excellence is what the track record of that center for publications is related to that disorder? And are they involved in clinical studies and clinical trials trying to fine tune or improve outcomes for these difficult problems?
And those centers that certainly have the higher case volume, regardless of what strategy is used, those centers that have the highest case volumes, publication rates, things like that are one way to help sort out what is the center of excellence.

PROF. KALAMARIDES >> I just would add -- you are totally right. I just would add it's important to participate in NF2 meetings to -- it's a small world, but you know, I think that people participating, we have a meeting every four years, NF2 state of the art. So where we discuss only NF2. Such attendance shows that people are very involved in nf2. It's a small field, but it's important to be there, so I would add this.
Sometimes, especially for radiosurgery, you have multiple teams, like 12 gamma knife centers involved, so it's difficult sometimes to know exactly the number of cases by centers. You are very famous for gamma knife, but sometimes it's difficult to know exactly the number of patients.

PROF. LUNSFORD >> yes, I agree.

MARY SELL >> very good. I'd like to give each of our panelists a few minutes, if you'd like, for some final thoughts and conclusions and then we'll also have Gilles

Go through some of the questions and answers that were submitted during this presentation. So I'll give you each a few minutes, and Gilles can read a few final questions that have come up during the presentation.

We'll start with you, Dr. Kalamarides.

PROF. KALAMARIDES >> yes, i think that the most important is to consider that NF2 patients should be managed holistically, so not only vestibular schwannomas, but they have to be followed. You need to know the natural history of every tumor before deciding to treat the tumor. Patients should be aware of all the possibilities of treatment -- surgery, radiosurgery -- and it's better to see the professional, not to discuss gamma knife with a surgeon who has no experience in radiosurgery, and the same discussion with a surgeon with experience not only with radiosurgery.
I just want to add something on malignancy we didn't discuss. I saw your presentation. We were recently at the European NF meeting, where Gareth Evans, a geneticist that's very famous for NF2, showed his experience in the UK where they can collect all the NF2 patients because they are organizing four centers, and they showed the experience of 30 years of follow-up. It showed that in their experience many -- can I share my screen?

MARY SELL >> yeah, there's a share screen button.

PROF. KALAMARIDES >> you see my screen?

MARY SELL >> yes.

PROF. KALAMARIDES >> so I add the slides that Gareth Evans gave me because it was interesting. They analyzed 266 patients irradiated by all the possibilities, not only gamma knife but the protons, and their results I want to go directly. 7.5% of patients treated by radiation, whatever the type of radiation, and over the last 40 years, so it's not recently, developed malignancy progression compared to only 2% of patients after the age of 26. This is a conclusion they observed radiotherapies associated with 5% of rate of malignancy. There is no VS MPNST reacted without radiotherapy. So it's rare, but it does exist. So in their experience, it is increased risk. Not so high, but there is a risk of malignancy, especially after radiotherapy, radiosurgery, proton beam therapy in the youngest nf2 patients.
So I think that that should be discussed. Like I say, it's not a no go, like for no surgery with gamma knife, but it's, I think, an interesting experience because they collect all the cases in one island, I would say. They try to publish the paper. It's difficult because it's a controversy. But I wanted to add this to the discussion.
Thank you.

MARY SELL >> thank you. Dr. Macdonald, do you have any last thoughts or conclusions that you'd like to share with the audience?

PROF. MACDONALD >> I want to say thank you to doctor Kalamarides and Lunsford, and I would reiterate it is very important for any patient with NF2 to go to a center of Excellence to have multidisciplinary tumor boards and make sure you have physicians that reach out to others with expertise in NF2 in the field and include them in the discussion. It's always great to get more than one opinion, and you should never feel badly about getting a second opinion. These are very rare cases, and there are often multiple options.
I do worry most about second malignancies, which is why I showed the slide on that, because a lot of patients with NF2 have very curable tumors, and they will live for a long time after the treatment of their tumors. Just like pediatric patients, even if you are older than 23, I would still worry about a malignancy that could be induced by radiation 30, 40, 50 years later.
Our outcomes often don't track patients for that long, even in the best clinical studies. So we use radiation therapy when we can preserve a function and there are no other options, but not routinely. For patients with NF2, we look for other options first. We also, again, recommend modalities like particle therapy or proton therapy, but minimize the dose to tissues that do not need to be treated in hopes of limiting radiation exposure.
So thank you again for the opportunity.

MARY SELL >> thank you, Professor Macdonald. Professor Lunsford, do you have any final words or thoughts for the audience?

PROF. LUNSFORD>> yes, in the sense that I think that individualized treatment for each patient is critical, and there is no one magic bullet that is the right treatment for every patient. And finally, I would say, while you're gathering information, try to gather it from centers that are working on this disease with scientific and academic publications. Please do not rely on social media or the internet to try to grasp what represents the latest and greatest treatment for this complex disorder. It is a field which stirs emotion, even in not only patients and families, it stirs it among doctors as well. Some doctors tend to have rather rigid beliefs about their certain strategy for management of this. If I found a doctor who had such rigid beliefs, I would very gracefully leave and find another doctor.

MARY SELL >> thank you. All right. We'll turn it over to Gilles now to read through some final questions that the audience had typed in during this presentation.

GILLES ATLAN >> yes. There are many, many questions, so we won't be able to take all of them, but I promise that I am going to share all the questions with the panelists, and hopefully the panelists will be able to answer to them later on. I have your E-mail, I have the e-mail of the people that are submitting Questions. We'll be able to get the answer.

So let's start with a few questions. Question from Elena from France. She has a young child with NF2. Is there a minimum size of tumor for proton therapy and a minimal age for the patients? For using proton therapy.

PROF. MACDONALD >> so for age, there's no minimum age, but the younger the patient, the more we try to avoid radiation in general. If you are using radiation, the younger the age, the more likely we are going to recommend proton radiation.
If you have a tumor that's very small, like a small vestibular schwannoma, it may be that a treatment like gamma knife is actually better than proton radiation because tiny, tiny tumors are difficult to treat with protons, if they are less than 1.5 centimeters. It might be a better treatment with Gamma Knife.

GILLES ATLAN >> could you define what is small. That is another question. What is a small tumor? What's the size?

PROF. MACDONALD >> a size of about a centimeter to 1.5 centimeters or smaller.

GILLES ATLAN >> thank you. Another question from C.J., are these type of treatments available to patients who have cochlear and ABI placements with magnets?

PROF. LUNSFORD>> I'll make one answer. The answer is that for many techniques where imaging is absolutely critical to define the target, these devices have a huge artifact, and some of them will require the removal of the battery or the device to be able to follow the patient clinically. So i think it has to be a very delicate balance between the benefit of these devices versus the likelihood that brain imaging will be seriously difficult to follow the growth of such -- or response of such tumors over time.

PROF. KALAMARIDES >> yes, we have patients with cochlear implant or ABI, and it's possible to do gamma knife. We have many cases like this. Sometimes the subcutaneous magnet has to be removed just during the procedure of the gamma knife, but it's quite possible.

GILLES ATLAN >> question from Nicole. Is it possible to treat only part of the tumor away from the nerve to control but with a goal to improve the hearing preservation? Is it possible to treat only part of the tumor?

PROF. KALAMARIDES >> it's difficult to see the nerve on MRI. So, no, it's a difficult thing.

PROF. LUNSFORD >> even with very small tumors, we cannot always see the nerve as it courses along or sometimes within the tumor. I think subtotal treatment has to be better defined, but lower dose in some centers has been used to try to have better hearing preservation rates. But in our experience, it has much less effectiveness as well in terms of tumor control.

PROF. MACDONALD >> it is sometimes possible to preserve the cochlea, which sometimes results in hearing loss at the time of radiation, but you wouldn't treat part of the tumor in order to do that.

PROF. LUNSFORD >> I agree.

GILLES ATLAN >> questions from Roland. With spinal ependymomas, will this type of radiation cause the tumor to swell, to increase in size after treatment?

PROF. MACDONALD >> it could. It depends on if the tumor is pressing on the spinal cord, how large it is, if that would be symptomatic or not. We do treat ependymomas frequently in patients without NF2, and generally we try to surgically decompress or remove as much as possible to avoid that complication.

GILLES ATLAN >> another question about proton beams from Barbara. Can the proton beam save the sight, save the vision if you have a tumor on the optical nerve?

PROF. MACDONALD >> yes, in certain situations it can help to preserve sight. So an indication for proton radiation would be a patient with an optic nerve meningioma and intact vision. In order to preserve function. Again, there's risks of radiation but also benefits. In terms of treatment of that type of tumor, that might be the only vision sparing option available.

GILLES ATLAN >> thank you very much. I think we are over time now, Mary. As I said, I promise to go over the questions and give them to our panelists so we can get their answer in the next few days.

MARY SELL >> very good. Thank you to all of our panelists for sharing your expertise. I learned so much listening to you, and I'm sure our audience did as well.

So thank you for your time and your expertise today.

PROF. LUNSFORD & PROF. KALAMARIDES >> thank you.

PROF. MACDONALD >> thank you.