



Company: Acoustic Neuroma Association
Conference Title: AN Regrowth: A Discussion of Treatment Options
Moderator: Melissa Baumbick
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Operator: Welcome to ANA's 2017 Spring Webinar Series and to our Fifth Annual AN Awareness Week. We've had a great week so far, sharing stories and pictures to inspire and inform. Today, we are excited to host a webinar on a topic that I think most AN patients think about at one time or another – tumour regrowth.

We are honoured to welcome Dr. Jennifer Moliterno and Dr. James Yu, both from the Yale School of Medicine, the Yale New Haven Hospital and the Smilow Cancer Centre. I am Melissa Baumbick, the Communications Specialist for the Acoustic Neuroma Association and your moderator today.

Before we get started, I want to let you know that all attendees are in listen-only mode and will remain that way throughout the webinar. There's a chat feature in the control panel on your screen and you can – that can be used to type comments or questions while Dr. Moliterno and Dr. Yu are speaking. On some browsers, that chat window is closed by default. To open it, please click the blue Talk bubble at the bottom-left-hand corner. We will dedicate the last portion of the webinar to answering as many questions as we can.

There will be a recording of this webinar that includes the audio and all PowerPoint slides available next week on the ANA website. There will also be a written transcript available. Please watch our website and social media sites for notification that the webinar has been updated and is available for viewing.

I would like to thank our webinar sponsors. Our presenting sponsors are the House Clinic Acoustic Neuroma Centre at St. Vincent Medical Centre and Vanderbilt University Medical



Acoustic Neuroma Association – AN Regrowth: A Discussion of Treatment Options Centre. And our supporting sponsors are NSPC Brain and Spine Surgery, University of Colorado Acoustic Neuroma Programme and Rocky Mountain Gamma Knife Centre, USC Acoustic Neuroma Centre, Keck Medicine of USC and Weill Cornell Medicine's Dr. Samuel Selesnick and Dr. Philip Steig.

As you know, this webinar is being hosted by the Acoustic Neuroma Association. ANA is a patient member organisation providing information and support to those dealing with acoustic neuroma diagnoses since 1981. Our programmes include a quarterly newsletter, patient information booklets and network of local support groups, our websites and social media sites and these informational webinars.

Recently, ANA launched its new Patient Registry, which is now live. This registry replaces the patient surveys we have done in the past. By participating, you are providing information to encourage medical research that will improve the lives of AN patients. To participate, go to the ANA homepage at anausa.org and click on the "Learn more and take the survey" button.

Finally, I'd like to introduce our speakers. Dr. Jennifer Moliterno is a board-certified, fellowship-trained neurosurgeon at Yale University. She underwent neurosurgical training at Yale and additional neurosurgical oncology fellowship training at the Memorial Sloan Kettering Cancer Centre in Manhattan. Dr. Moliterno is specialised in the surgical treatment of all types of brain tumours, with particular expertise in the management of acoustic neuromas.

While Dr. Moliterno is facile with the various microsurgical approaches and techniques for removing these tumours, she employs close observation and performs Gamma Knife radiosurgery when indicated. As such, she routinely sees patients with ANs and is frequently referred patients with larger, more complex tumours and those who have had treatment and subsequent recurrence.



Dr. Yu is the Director of the Genitourinary Cancers Radiotherapy and Co-Director of the Gamma Knife Programme for the Department of Therapeutic Radiology at the Yale School of Medicine. Dr. Yu's research centres on the comparative effectiveness of new radiation technologies and how these new technologies are adopted nationally.

He is currently a Yale Centre for Clinical Investigation scholar and member of the Cancer Outcomes, Public Policy, and Effectiveness Research Centre at Yale. He is also a Senior Editor for the journal of *Practical Radiation Oncology*, and is on the editorial boards of several other publications.

It is now my pleasure to get started and turn the webinar over to our presenter. Dr. Moliterno, please go ahead.

Dr. Jennifer Moliterno: Thank you, Melissa, so much for that nice introduction. Thank you to James for being here with me. And then, thank you to everybody else for listening to this webinar. And so, we will get started. You can hear me okay, I assume?

Melissa Baumbick: Yes, so far.

Dr. Jennifer Moliterno: Okay. Good. Okay. All right. So, I have no disclosures. Dr. Yu's is listed. And all the patients that we're going to present gave their consent to their photos and their information being presented as well.

Though Melissa gave a really nice introduction, just a little bit about me. As she mentioned, I trained here at Yale, went to Sloan Kettering for fellowship training and then came back to Yale where, again, I specialise in all types of brain tumour surgery. But especially – sorry, I'll talk louder. I see the comments. But I specialise particularly in acoustic neuromas. And just make some comments if you can't hear me.



So, just some basics to start off, in case anybody listening is also listening for newly diagnosed acoustic neuromas in terms of the management and, then also, just so we're all on kind of the same page. So, acoustic neuroma, also known as vestibular schwannomas, are usually benign, not cancer tumours and are usually not associated with any syndromes or higher risks of developing tumours. Nonetheless, it's understandably a very scary diagnosis. And the reason why is because these tumours present near very critical structures in the brain.

And some of those, as you know, we'll discuss are cranial nerves VII and VIII – VII being the facial nerve with a nerve that controls the facial function, motor function, VIII being the one that controls hearing and balance. Other cranial nerves for facial sensation and swallowing as well as, of course, arteries – important arteries. And, of course, the brain stem.

So, in terms of management, the basics really for the initial management options for acoustic neuromas and, then also how we manage regrowth are basically observation, meaning that we follow patients closely with serial MRIs, meaning that we schedule MRIs every so often; radiation, which Dr. Yu will talk about a little bit more than me, and then also, of course, surgery. And there's various approaches that I'm sure everyone is familiar with at least hearing about.

So, when to treat? Even initially – and again, we'll get to regrowth momentarily. But when to treat acoustic neuromas can be very clear-cut or it can be more ambiguous. And so, there's many factors that come into this. And so, size is one for sure. Patient-related factors: how old is the patient, medical conditions, how healthy is the patient to withstand surgery, for instance. Symptoms – whether or not, you know, this is found by chance or the patient is actually symptomatic from the tumour. And then, of course, taking into consideration the person's wishes and preferences.



And these cases, again, can be clear-cut and then they can also be more ambiguous. And certainly, cases of regrowth can be more ambiguous and really requires a thoughtful type of management. So, I can't emphasise enough for initial diagnosis and then also, especially for regrowth and recurrence, it's important to seek consultation with somebody who has experience. And it's usually a team of physicians who work together.

But would – this actually is a picture of me talking with my colleague here with Jill and Pete Myers and I'll actually present one of these patients later. But it's very important to see people who regularly see patients with acoustic neuroma. I would advise to ask for numbers – how many people do they see, how often do they see patients with acoustic neuromas.

Ask what other types of surgeries he or she performs or what other types of radiation that he or she performs. Especially with surgery, this is a very technically challenging and complex type of surgery. And there's very few people who do this type of surgery and do it well. So, it's important to seek consultation with those people. And again, also ask how many he or she has done in the last month, last year – that sort of thing.

In addition, typically – these types of surgery can typically be done at academic institutions. So, again, we're talking about a multidisciplinary team of specialised physicians. Often, they're fellowship-trained or they have sub-specialised training in brain tumour surgery, such as myself, who work with other types of doctors, such as Dr. Yu, to take care of patients with acoustic neuromas.

This is a picture of our intraoperative MRI here at Yale. So, often times, you're looking at places that have state-of-the-art technology and that sort of thing, in terms of being able to really treat these types of tumours. It's important to find consultation with people who are capable of weighing in about all the treatment options, not just biased towards one; someone who does



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surgery, but also does radiosurgery so they can give you a thoughtful perspective, especially for regrowth, in terms of the management options that you have.

Second opinions are usually very helpful and I highly encourage them. I think that it's always important for patients to feel comfortable, in terms of what their plan or management is. And so, opinions can vary, especially with regrowth, as we'll discuss. But often times, people are saying the same – similar things, rather, in different ways. And so, this is not the focus of this discussion, but just, again, to get everybody on the same page.

And as a surgeon myself, I feel compelled to mention. So, for surgery where there's various approaches, each has its own pros and cons which, again, is not the focus of this talk. But you might be – you know, hear retrosigmoid approach, translab approach. Middle fossa is less commonly done for various reasons. But those – retrosigmoid and translab – are the main ones.

The goals of surgery in every case is to control the tumour. And so, we always try to get as much of the tumour removed as possible the first time around, as safely as possible. Of course, it's – with larger tumours, there's brain stem compression. That's one of our main goals, is to decompress the brain stem. And then, facial nerve preservation is always of utter importance to us. And I'll go through that a little bit more, in terms of surgical strategy. And then, of course, hearing preservation. We always attempt that when it is possible. But that is a little bit trickier, especially with larger tumours.

Neuromonitoring is another buzzword you'll hear about. And that's something you want to be sure the surgeon has mentioned because that should be standard on all cases – monitoring of those nerves and also the function of the brain stem and, you know, motor evoked potentials and sensory as well. Neuronavigation you might hear about, but that is not necessary on these cases. But, of course, you know, the larger centres, the surgeons who do these more commonly will have access to that.



Again, in terms of the initial surgery – and then, of course, for regrowth, this applies too – the goal is to remove as much tumour as safely as possible. Again, we want to aim to decompress the brain stem if there is brain stem compression. We want to gain tumour control. And so, our goal is to not have it grow back or come back. And to preserve function and quality of life. And what I mean by that is the function, particularly of the facial nerve – of the motor function of the face as well as the swallowing nerve. With larger tumours, those can certainly be involved.

It can often be a balance between removing more tumour and preserving function. And so, it often becomes a call – a judgement call, really, in the operating room. If the tumour is quite stuck to those nerves, it's possible that we might actually leave a small amount of tumour on the facial nerve to preserve its function. And again, this become more relevant in terms of regrowth, which we'll get to.

So, this is a patient of mine, a 59-year-old who, otherwise healthy, had some hearing loss, had some abnormal facial sensation on the right side with significant balance issues that were interfering with work and such. And he had been worsening for the last year or so. We ended up doing a right retrosigmoid approach on him a little over a year ago now. And here he is. And actually, after surgery, his face looked great. He had minimal, if any, facial weakness. But as you can see in his MRI over here, he left – we left a small amount of tumour that was left on the facial nerve to preserve its function.

So at this point, we're following him with serial MRIs, meaning that, you know, we're scanning him every so often and keeping an eye on this residual. And this is his most recent scan here. So the question becomes, just like in that case presentation, what to do for a residual tumour. So in capable, experienced surgical hands, a small amount of tumour, as I mentioned, may be left behind on the facial nerve and is left behind for a good reason. As I tell my patients, I can make any scan look perfect, but you may not want me to do that because I can certainly risk a



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permanent injury to the facial nerve. So – like again, it becomes a balance between removing as much tumour as we can at the time of surgery and preserving facial nerve function.

It's encouraging because the pathology is usually benign and slow-growing, which is a good thing and certainly in favour of us taking this type of approach for surgery. But nonetheless, even a small amount of tumour can still grow. And as the literature has shown us, there's really no good way to predict which – you know, in which patients the tumour will grow and in which patients they won't.

So, what do you do about the residual tumour? So, we go back to the basics that I talked about in terms of the initial management. And so, observation, radiation and surgery. And this, again, depends on several factors which is very similar to the factors that were playing into the initial management of the tumour.

Added to those – which again, you know, typically is size – how much tumour was left behind – is that the actual tumour or is it just a capsule that's stuck on to the facial nerve or the brain stem, for instance. Of course, the patient's age and medical condition, how they're doing in terms of postoperative recovery? And so, if there was some temporary facial weakness because of manipulation of the facial nerve, it might be best to kind of give the nerve some time to cool down a little bit before introducing another type of treatment.

And then, another, which I skipped over here, is really the reason for leaving tumour behind. And so, as a surgeon, I know whether or not I'm able to remove more. And if I leave tumour behind, I'm usually leaving it for a reason. So, it's either that it's too stuck to the facial nerve, there's just no playing. In fact, last week, I had a case where the tumour just disappeared into the tumour. And so, I had to stop. And so, I corded out as much as I could, but left that capsule of the tumour because I could not trace the facial nerve anymore. Or, there's sometimes where the exposure –



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because of the patient's anatomy, it might be limited with just one approach. And so, maybe coming back with a different surgical approach is a viable option.

And so, I tend to favour – usually favour, I should say – and everybody is different. Every patient is different, I should say. I usually favour observing. And the reason why is actually several. First of all, the benign pathology is very reassuring. The tumour can actually sometimes regress even after surgery, when the dust settles and things kind of settle down. You'd be surprised that the tumour can actually get smaller – or the post-op changes, I should say, can get smaller with time.

And I usually, again, use this in patients who have a relatively small residual tumour. I also tend to favour this in patients who are older because, of course, you know, there is – there's smaller growth over 'x' many years of the patient's life, and particularly those who have any transient facial weakness after surgery – again, giving time for the nerve to recover.

Again, unfortunately, there is no good way to predict which tumours will grow and which won't. And so, that's why it's important to follow these closely with serial MRIs. So, I usually get it – an MRI at three months after surgery. If I'm a little bit more concerned, I'll continue to follow three months or so. I tend to be conservative with that. And then, I'll stretch to about six months and then to a year, etc., depending on how the patient is doing and how the tumour looks, in terms of the MRI scan.

If it grows, we're able to pick it up early and then we can intervene early. And it's very important that – again, these tumours – these surgeries are typically done at academic centres where we have tumour boards. And there are multidisciplinary tumour boards. So, people like myself and Dr. Yu, and neurooncologists, neuroradiologists, neuropathologists – all come together and talk about patients with not only acoustic neuromas, but also other types of brain tumours and make the joint and collective decision how to treat patients.



In terms of more of what to do with residual tumour at the time of surgery, sometimes we will opt to do upfront treatment. So, we won't even give the residual tumour a chance to regrow. We'll just go ahead and treat it. And so, rarely – very rarely, will I ever plan a staged approach. I usually try to – and I am usually pretty successful at tackling the surgery in a one-setting type of a surgery.

But sometimes, really large tumours are such, you might hear a surgeon hear they want to do a staged approach or they might do a combined approach. So, they might start out doing, for instance, a retrosigmoid and then come back doing a translab because, again, it gives the surgeon a little bit of a different anatomical exposure. And so, that's one case where I may just go ahead and just do it and not wait for the tumour to grow.

And then also, radiation. And so, for instance, if we're talking about a younger patient and I've been in there and I know that the tumour is a difficult consistency, difficult to work with and, you know, the facial nerve wasn't tolerating the manipulation, then what I might do – and especially, like I said, with younger patients – I may, you know, call up James and say, "Hey, what do you think about this?" And again, present the patient at the tumour board and seek consultation with radiation on the earlier side.

What to do when the residual tumour actually grows? So, these are for the patients that we observe. And I saw a quick question over here, "How long, you know, will you follow tumours with MRIs?" That, again, depends on the size of the tumour – how much is left and that sort of thing. And I'll show you some patient examples where I can give you a little bit of a better number to that.

So, regrowth after surgery. Again, if I'm in there – and again, if you have a surgeon who's capable, a surgeon who's used to doing this surgery and, you know, is experienced with this type of surgery, he or she left tumour there for a reason. So, you always have to tell yourself that. If



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there's any question as to whether, you know – how – whether the tumour was left for various reasons, then it's always best to get another opinion. It may – can never hurt.

But anyway, if the tumour was left there for a specific reason like I mentioned, then with regrowth after surgery, I would tend to favour towards radiation. And again, I know, having been in there, that the chances of me doing anything to get more tumour out is probably not that great. The only caveat to that where I may recommend surgery, if there's regrowth, if the patient is symptomatic.

And so, if there's compression of the brain stem, for instance, and that really needs to be debulked and the only way to do that is through surgery. And if the patient is having imbalance or, you know, dizziness or something where I think going in there surgically would help, then I would err towards the side of doing additional surgery.

But usually, I would favour going down the radiation route. And again, the tumour growth, often times – because only a small residual is left the first time around – it's usually confined to the ear canal. And so – which is the IAC. And so, that is usually a very good target for radiation. And James will speak more to that.

It's important to understand that when you talk about surgery after regrowth and especially surgery after surgery or surgery after radiation after surgery, etc., facial nerve preservation becomes more and more difficult. And it becomes more challenging with subsequent surgeries. And the balance, as I mentioned before, between removing as much tumour as we can and preserving function can definitely start bending towards the other way, meaning that if we see that there is a tumour that's progressing quite significantly and growing despite surgery and radiation, for instance, then we may have to become more aggressive from a surgical standpoint, which really may put the facial nerve at risk. But, of course, we don't do that unless we're at that point. And, of course, with the patient fully aware.



Regrowth after radiation or stereotactic radiosurgery. So, I see quite a bit of these patients. I – usually, what happens is patients will see physicians in the community – doctors who're a little bit or surgeons, I should say, who're a little bit less familiar with removing these types of tumours. And so, they end up to favour giving radiosurgery because, you know, it's non-invasive and it's an outpatient procedure and it's certainly less challenging than the surgery.

Having said that – and James forgive me – but radiation, although it's not invasive, it doesn't mean that it's not without potential issues or complications and that includes regrowth. And so, it also definitely makes surgery more challenging. It's not impossible, but it makes it more challenging. And the risk to the facial nerve and to weakness is definitely greater after someone has been treated with radiation and then they experience regrowth. And so, again, it's not impossible, but it usually means that the recovery of the facial nerve will take longer.

And so, here's actually a patient of mine. And so, this is a 68-year-old, otherwise healthy, yacht salesman who has this tumour here, which I think you can see was back in 2012. He had some hearing loss. He saw another neurosurgeon in the community and they performed radiosurgery. This is 2014. He started having some worsening symptoms – some tinnitus, some vertigo, etc. And you can see it's larger. There's some more mass effect on the brain stem over here.

And then in 2016, he was referred to me. Definitely larger, more mass effect on the brain stem, even a little effacement or a shifting of ventricle here. And so, we opted – and I'm sorry, by the time he came to see me, he was having facial twitching. And so, he was having more facial nerve symptoms, which is always a sign that the recovery of the facial nerve after surgery is going to be longer.

And so, we opted to do a translab approach, which I sometimes do in these cases after regrowth because it allows me to identify the facial nerve early on, which, you know, in my mind, helps



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protect it a little bit better. And so, this is him a couple of months ago. Actually, he's about seven months post-op here. His facial weakness significantly has improved.

We had to leave, again, a small amount of residual – more than I probably would have liked – on the facial nerve. But that's what we needed to do to make sure that the nerve was intact. And so, what we'll do, since he had radiation before, is we'll just follow him – again, with MRIs. And then, of course, present him at our tumour board and that sort of thing. But he'd doing quite well.

Another lady, a 49-year-old woman, who similarly presented with hearing loss in 2011. She underwent stereotactic radiosurgery by another neurosurgeon. This was her scan. Actually, this wasn't her original scan. This is her kind of more recent scan. And then in 2015, when this scan was from, she ended up having complete hearing loss. She was referred to me because she became symptomatic, meaning – more symptomatic, I should say. She had facial numbness which was getting worse. And she came to me for a second opinion and ended up coming to me for surgery.

We also did a translab approach on her as well. And so here, she has – we were able to get a really nice resection on her. Her face, again, was weaker than I would have expected for that size tumour, but it was because it was more stuck to the facial nerve. And we're following her with serial imaging.

And so for her MRI, to answer that question before, I would probably follow her – I would probably lengthen the time to follow her longer than I would for the gentleman before because there's less tumour residual there. And again, I tend to be more conservative in terms of follow-up. But I certainly negotiate with my patients as well, in terms of that.

This is a patient of Dr. Pete Myers who I showed a picture of – my colleague here at Yale, which was just emphasising the fact that, you know, there's no perfect solution. It sometimes requires



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you to be thoughtful. And it requires you and the patient to really just have a good relationship and good communication.

And so, this was a patient of his. I believe she's 73 now. So in 2012, she had this tumour. He ended up doing surgery. He left some residual on the facial nerve and ended up – again, it had remained stable, but then I think it grew a little bit from what it was post-op. And so, he ended up doing Gamma Knife in 2013. In 2014, it remained stable, for the most part, in size.

And then in 2015, it showed growth. I think concurrently, she was having a little bit of numbness on her face. But she opted just for observation. And actually – and to be honest, I'm not sure if he recommended something over the other or they both jointly decided to do observation. And then in 2016, it showed some regression.

And so, that is possible that – for after treatment, for these tumours to regress. And so, I think that there really is a role for observation. And then also, you know, there's only so many times that you can really use surgery and radiation, as I'm sure James will get to as well. And so, knowing when to use the treatments, I think, is important as well and not just jumping the gun to treat.

And so, now Dr. Yu will take over.

Dr. James Yu: Great. Thank you, Dr. Moliterno, for – and I actually learned a lot during that half-hour because as a radiation oncologist, I obviously can't perform any sort of surgery inside the brain.
And –

Dr. Jennifer Moliterno: I always invite you to come.

Dr. James Yu: That's really –



Dr. Jennifer Moliterno: No, sorry.

Dr. James Yu: But it's – to hear the surgical considerations very helpful. So, I'm going to talk about the role of radiation for acoustic neuromas and mainly – or vestibular schwannomas. And mainly, what I'm going to talk about are those that occurred after surgery. And then, briefly, I'll touch upon those that recur after radiosurgery and maybe we can discuss that even in the question period.

So, a little bit about me. I trained in – I went to medical school at the University of Michigan. And I trained here in radiation oncology at Yale New Haven Hospital. And I'm interested in not just new radiation technologies, but whether these new technologies are any better than the old ones. Because often times, we invent things that may not be better than the things that we've been using all along.

So, I'm going to talk about two major types of radiation therapy and these are both what's called teletherapy or beamed radiation. One is called stereotactic radiosurgery and a small part of that is what's called fractionated radiosurgery. And then, I'm going to talk about fractionated stereotactic radiotherapy. And so, it's a little bit of semantic game. But radiosurgery indicates the use of two things. One is stereotaxis, where the patient is localised precisely in 3D space. And also, very high doses of radiation delivered in one up to five treatments.

Fractionated stereotactic radiotherapy also uses stereotaxis or localisation in 3D space, but it's not as rigorous a localisation. And also, you break up the treatments a little bit more. So, the advantage of stereotactic radiosurgery is it's more precise. It's typically one treatment, especially for acoustic neuromas. And there is what's called a tight dose distribution, meaning we really try and not go beyond about a millimetre of the defined tumour.



The disadvantages of stereotactic radiosurgery are that the radiobiology may not be maximised. And what that means is there's decades of research into how the normal brain, normal nerves and tumours respond to different doses of radiation given over different amounts of time. And it's theorised that if you break the radiation up into smaller pieces, there's a greater therapeutic ratio because the normal tissue is able to repair itself in between radiation doses whereas tumour or other aberrant growth is not able to.

So theoretically, you maximise the therapeutic ratio if you break the treatment up. That said, if you're going to do a Gamma Knife treatment or some sort of treatment where you have to attach a frame onto the patient's head, you don't want to do that 28 times. And hence, that's why radiosurgery has developed into a single large dose or maybe a couple large doses.

Fractionated stereotactic radiotherapy, on the other hand, may maximise radiobiology. But it also delivers a greater integral dose to the normal brain – normal tissue, skin, skull, etc. The advantages are it's a little bit more forgivable to large error margins. Because if the patient is off by a couple millimetres for one treatment, you know, if you have 27 treatments that are spot one, then theoretically, there is less, you know, problems to the patient than if you're off one out of three treatments, for example.

The disadvantages of stereotactic radiotherapy are rather than a frame, we use what's called a – an aquaplast mask, which is a mesh that is plastic. It's – it becomes flexible if you heat it. But if it cools and comes to room temperature or body temperature, it is rigid. And so, this mask goes over the patient's face and then forms to their face. And typically, it also comes under their head as well. That can feel, sometimes, more claustrophobic than the headframe. The advantage though is that you don't have to screw anything to the skull. So, it really depends on the patient which treatment that they would prefer.



Another disadvantage of radiotherapy is you do have to come repeatedly 25 to 28 times and we've already discussed that. There may be greater normal tissue dose. And therefore, there may be – and there likely is a greater risk of having cancer created by the radiation treatment. I see a lot of questions about CyberKnife and Gamma Knife. We'll get to those.

So, this is a table that looks at the studies that I could find looking at the efficacy of radiosurgery for a tumour that has recurred after surgery. And you can see that the numbers are quite good in terms of the outcome. 94% to 100% control at pretty long-term follow-ups – five to ten years of follow-up. And these were done with various types of radiosurgical platforms. But the longest ones that I've seen have been with the Gamma Knife because that technology has been around a little bit longer for radiosurgery.

Now, what about side effects? The side effects from radiosurgery are not to be minimised. But a lot of these folks have already had surgery to remove their vestibular schwannomas in the first place and now are getting a repeat treatment. So, there is, often times, some new facial nerve deficit or weakening. But actually, the numbers are relatively low. I was a little surprised about how low they were – you know, anywhere from 3% to 14% new facial nerve or new trigeminal nerve deficits.

What about fractionated radiotherapy? Well, these efficacy numbers look pretty good as well. However, the follow-up times for these are a little bit shorter and the numbers are a little bit smaller. So, this indicates that this fractionated radiotherapy is actually a newer technology than the Gamma Knife. And it's unclear how much better or how much worse the treatments are. I just think that they're different. And it's a different philosophy, in terms of how to approach the problem of a recurrent tumour.

Toxicity-wise though, as we talked about, theoretically, there's a greater therapeutic ratio with a fractionated treatment. And these numbers, although not directly comparative, seem to be, you



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know, on par with the radiosurgical treatment. So when you compare the two, it's unclear, really, which treatment is going to be better.

And that's the focus of my research is trying to figure out which treatments are better. And I don't have any answer for the folks on this call. I can only say that the track record is longer for radiosurgery, that the Gamma Knife has been around longer. And hopefully in the future, we will have studies comparing these two.

Fractionated radiotherapy is theoretically, and only theoretically, better at preserving cranial nerve function. But again, looking back at the Gamma Knife data and the radiosurgical data, the radiosurgical treatments seem to be doing a pretty good job to begin with. So again, it's unclear. And I hope that I'll have an answer for you in a couple years.

So, how is radiosurgery done? Again, consultation with a neurosurgeon and a radiation oncologist is key. It's great to be here at Yale and have someone like Dr. Moliterno to send patients. Because sometimes, as a Gamma Knife centre, we get patients from outside neurosurgeon and outside radiation oncologists as well. And the first thing I do is to send them to Dr. Moliterno.

And this is a one-day treatment. Patients get the headframe placed. They get MRI planning scan on the day of the treatment. We do the treatment planning immediately adjacent to the Gamma Knife treatment room. And then, we deliver the treatment and then we remove the headframe – all in one day.

Now, what about CyberKnife? And what about Linac? And what about Gamma Knife? And what are these different machines? Well, they're all trying to deliver a focused dose of radiation to a single spot using multiple overlapping beams. That – you know, that's what they're all trying to do.



The Gamma Knife has over 190 radioactive sources emitting a pencil-thin beam – sometimes, a pencil-lead themed – thin beam through over 190 holes basically overlapping in a single spot. The machine is very robust because all those sources are welded into place. And there's very little inaccuracy in the treatments themselves because there's so few moving parts.

The CyberKnife attempts to mimic the Gamma Knife in – basically, it's trying to make multiple overlapping beams in a single spot. The nice thing about the CyberKnife is they can treat other parts of the body. The Gamma Knife is dedicated to the brain and skull base whereas the CyberKnife can treat multiple places on the body. And rather than treating from over 190 angles at once, it treats from a single angle all at once. So, it basically moves that beam into position and mimics the Gamma Knife.

And on the bottom is what's called the linear accelerator, also attempting to put multiple overlapping beams into a single spot. And one of the innovations of the linear accelerator is we can now deliver treatments using a continuous arc of a beam. So, if you imagine, rather than using static angles overlapping, you can now use overlapping arcs where the focal point of the arc now becomes the high-dose region. And so, the treatments can be a little bit faster with the linear accelerator.

No one has compared all of these machines to each other. They each have their own distinctive advantages and disadvantages. At Yale, we do rely on the Gamma Knife for the stereotactic radiosurgical treatment of recurrent acoustic neuromas mainly because it's a dedicated machine. But other folks around the country do use these other two machines. They're all trying to do the same thing.

So, what about fractionated radiotherapy? Well, that's a different way of going about the treatment. You have a consultation with a radiation oncologist. Again, if you haven't seen a



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neurosurgeon, I also send you to a neurosurgeon for an opinion. You get what's called a CT simulation where they make this mask that we talked of. Then, you wait.

You wait a couple weeks while the radiation oncologist and all the staff at the radiation oncology centre does their homework, combining the MRI that you've had – and if your MRI is no good, we'll get another one – and with the planning CAT scan. And then, once your radiation treatment plan has been created, multiple physicists then verify that the treatment plan makes sense. A second physicist verifies that the first physicist was correct.

And then, the therapist on the machine then – it's kind of like an airplane taking off. Everybody checks off that everybody – that quality control is there. And only then will you get your treatment, typically Monday through Friday or five to six weeks of daily radiation treatment. Once a week, you'll check in with a radiation oncologist just to make sure everything is going fine. And of course, there's nursing staff and radiation oncologists and therapy staff available. We even have social workers, nutritionists who are available if you need help during the treatment itself.

So, before – oh, I'm going to move back. So before we move to that summary slide, I'm going to talk about re-irradiation after radiosurgery because I think there was a question in there, "How many times can you do Gamma Knife? How many times can you do CyberKnife, etc.?" There's no good answer. But the rule of thumb is time is safety.

So, the longer you've had since your first radiosurgical treatment, the safer it is to deliver the second radiosurgical treatment because your body does recover. That facial nerve does recover a little bit – not completely, but a little bit – from the radiation treatment. Off the top of my head, I would preferably wait five or six years, honestly, since the first radiosurgical treatment to feel good about delivering a second radiosurgical treatment. The doses we use from a radiosurgical side are actually a little bit less than typical for, for example, a malignant type tumour. So, there is room to re-treat.



I have one patient that we treated three times because they had radiosurgery way back in the early days of the Yale Gamma Knife. And then, I think it was about eight years later, there was some very slow regrowth. The patient insisted on Gamma Knife. They didn't want surgical resection even though that was the recommendation. So, they had Gamma Knife again.

And then about eight years later, it grew again. Patient didn't want surgery or couldn't have surgery, so we did the treatment for the third time. That patient doesn't have any hearing function in that ear as a result of those three treatments. They have a – I think they had some transient facial nerve deficit, but otherwise were doing pretty well. And the lesson I learned from that was definitely the longer you go between treatments, the better and safer it is.

And I think that is the end of my slides and I'm going to pass it back to Jen.

Dr. Jennifer Moliterno: So – thanks, James, so much. So, in summary, we treat when we need to. And we reserve our options for treating when we're pushed to treat – the patient is symptomatic, regrowth is evident, etc. We aim to treat the tumour as best we can the first time, but again, while being as safe as possible, meaning that we aim to preserve the function and the quality of life of the patient.

The current surgical strategy, again, is to leave a small amount of tumour on the facial nerve to preserve its function. And there really is nothing to suggest which tumours will grow and which will not. And so, that's where it really becomes very much a case-by-case basis with you, along with your physician, to monitor this.

Again, I saw one question just quickly about, you know, "When do we treat? When do we observe?" And I would say for the majority of cases, I usually will observe – again, because there's typically small amounts of residual. But if there is – you know, if there's residual brain



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stem compression, if patients are still symptomatic, if it's a younger patient that I know it was quite stuck to the facial nerve and I know that additional surgery that I'm not going to do any better with removing the tumour while preserving function, then those, we might be more apt to treat instead of waiting for the residual tumour to grow in those scenarios.

I think it really, again, comes down to having a team of physicians that you feel comfortable with, who are thoughtful physicians, who are used to seeing these types of tumours and not only seeing these types of tumours, but treating patients with these types of tumours – not just following them, but really treating them. And that's where the decision for what to do with residual tumour and regrowth is important.

Future directions – again, just here – just touching on it very quickly, here at Yale, we do genetic sequencing of all our brain tumours. And this allows us to understand the mutations of these tumours. We can do comparisons of tumours that do grow compared to those that do not. And the goal of it is ultimately, to find some sort of a drug target or a medical target. Because right now, what we have is going back and forth between observation and surgery and radiation. And then, just going back and forth between those. So ideally, in the future, it would be great to have some sort of a medication or some sort of drug target and that's what we are working on.

And again, I can't emphasise this enough, everyone is different and it's really important to tailor the management approach to the person themselves. And it's really, I can't emphasise enough, important to have somebody who does this routinely and regularly. And so, I'm very happy to – again, James and I see patients with acoustic neuromas all the time. We often offer second opinions. And so, more than happy for any of you to reach out. You can reach out to me and I can, you know, triage it from there. My office number is there. My e-mail is there. And we can go from there. And these are children, which is our pride and joy, and what we do in our spare time. So, thank you so much.



Melissa Baumbick: Thank you both for a really informative presentation. And I really appreciate you going through and even answering some of the questions as you were sort of talking through your presentation. We have a couple minutes and I'd like to ask you just a few questions, if we can.

One of the questions that I received was, "How much regrowth are you seeing with your patients? Is it significantly more than it used to be, is it less? And what are you seeing sort of on a trend basis?"

Dr. Jennifer Moliterno: So, I think for the most part, I think it's less. I think that – again, you know, we – especially when we are referred the patients who have, you know, smaller tumours – again, a lot of times, you have to keep in mind too as a tertiary centre and as a centre with expertise in this, we often get patients who have been operated on before or they have larger tumours or more complex tumours and that sort of thing. So, that is kind of a little bit of different category.

But for more the straightforward kind of acoustic neuromas, I think that for the most part, you know, we're not seeing that much regrowth. Often times, we get a nice resection. There is a decent plane between the tumour and the facial nerve, and we just follow it from there. And again, you know, extending the period of time in the MRIs for observation.

Melissa Baumbick: Okay. And then, I have a question that could probably be answered by either of you, but maybe Dr. Yu. "When a patient has radiation to treat their acoustic neuroma and there is swelling then after the radiation, how do they know – when is it – when is the time to determine whether any regrowth is swelling or if the tumour is actually growing?"

Dr. James Yu: Right. So if we had a great test for that, we would be very famous. So, we don't know. It's very, very, very difficult to tell post-radiation swelling from tumour regrowth. Probably the key would be when the tumour regrowth or swelling occurred.



I would guess that a tumour that started to get bigger two, three, four years after treatment is more than likely growth whereas a tumour that swells a little maybe nine to 16 months after treatments is more likely to be treatment effect. But – mainly timing. And often times, there's nothing you can do anyways except to watch it. And then at some point, it will become symptomatic or need resection or Dr. Moliterno will kind of use her expertise and decide when the tumour needs to come out.

Dr. Jennifer Moliterno: Yeah.

Melissa Baumbick: Okay.

Dr. Jennifer Moliterno: And sometimes, it again just comes back to going back and forth. You know, again, just –

Dr. James Yu: Right.

Dr. Jennifer Moliterno: – talking. You know, talking to each other, talking to the patient, etc., to really understand what the best plan is for each person.

Melissa Baumbick: Okay. We've had a couple patients talk about the fact that they've done their follow-up MRIs and they're – when they look back, there's – there were signs of regrowth there. But they weren't told about it at the time or on early post-surgical MRIs –

Dr. Jennifer Moliterno: Sure.

Melissa Baumbick: – there was nothing done. So, is there any kind of specialised – does – do reading those follow-up MRIs require specialised interpretation?



Dr. Jennifer Moliterno: No. So, I always read my films myself. So, as I mentioned, we have this multidisciplinary tumour board. We have a neuroradiologist, who I think we both trust very much. And so, he is my go-to guy whenever I have questions or concerns on MRIs. But I never really read the report from the – you know, whatever radiologist read it because I'm used to seeing these myself and used to looking at them myself.

I also tend to be the kind of person, which is probably different than most surgeons, that I don't have such a huge ego. And so, I would be more apt to say that I left tumour when I didn't really leave that much tumour whereas, you know, some people might say, "I got it all." And then, you know, you come to find that there was residual. And so, I think it's just different personalities and different approaches. But I just tend to be a little bit more hard on myself I guess is the way to say it.

And so, you know, it's definitely possible to remove it all, for sure. But again, especially when you're dealing with larger tumours, it just gets much more difficult to get a plane with a facial nerve just because the tumour has likely been there longer and has manipulated the nerve longer. And so, what I also do is whenever I see patients, I always show them their films. And it doesn't – you don't have to be a brain surgeon to read an MRI.

And there's just some basic steps. But it's the truth. You don't. And have them show it to you. And have them compare the before and the after. And if you see something that, you know, looks bright white, then that's probably some tumour there. And so, I always try to be as transparent as possible. And I would just recommend, you know, asking your physician to be the same.

Melissa Baumbick: Okay. And we are getting close to the end, so this will probably have to be my last question. But kind of on that vein, when – and I'm sure it is dependent on how much tumour is left, but when do you start to think about treatment as far as regrowth? What amount of regrowth is significant?



Dr. Jennifer Moliterno: So, I think, you know, various factors. So, taking into account the trend of the regrowth. And so, if we're watching it – and this is even the same for initial treatment of tumours, you know? I think I saw a question in there where someone had kind of an increase in size in a short amount of time. That would make me pay attention and repeat the imaging sooner so I could see if this is just something that's happening or is this really real and it's really taking off, for whatever reason.

And then, you know, whether or not the patient is symptomatic. The things that can really hurt a person are brain stem compression. That's the thing that really gets my attention. And so, you know, if there's regrowth and it's confined to the ear canal, that's not such a big thing to me. If it's really starting to push on the brain stem and it's starting to have more effects like that, then that certainly gets my attention more. And that, to me, would push somebody more into a surgical category.

Melissa Baumbick: Okay, great. Well, that does it. We are at the end of our time today. So, that'll have to be the last question. I want to thank Dr. Moliterno and Dr. Yu for taking the time to speak to us. And I want to thank everyone that has attended, both members and non-members of the Acoustic Neuroma Association. I hope that this has all been really helpful. A recording and a written transcript of the webinar will be available on our website next week.

We're right in the middle of Awareness Week. And this year has been really focused on mindfulness and quality of life. There's a lot of information on the website and on our social media sites about ways to heal your mind and your body as well as get involved in Awareness Week. So, make sure you're following us.



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And also, please mark your calendars for 8th June at 3:00 p.m. when Dr. Mark Eisenberg, the Chief of Neurosurgery at Long Island Jewish Medical Centre will present a webinar on headaches. Watch our website and our Facebook page for details and registration information.

And don't forget to participate in our new active Patient Registry. It's on the website. Thank you and have a great afternoon.