[MUSIC PLAYING]

MICHAEL MCDOWELL: Hi, everyone. My name is Michael McDowell. I'm the Director of Cranial Base Surgery and Vascular Disorders here at Children's Hospital of Pittsburgh. And today, I'm going to just go through some of the unique aspects of treating pediatric patients with complex neurosurgical conditions through the endonasal approach. These are my disclosures. None of them are related to the topics that we're discussing today.

So there's this classic phenomenon where people really often will say that children are just small adults. And we all know that is not the case. But in skull base, it really is an enormously magnified because of the tremendous differences in the pediatric skull base versus a mature adult skull base and because of the considerations that are related to the smaller size and the higher level of growth factors in children. So it's a very rare disease that's very poorly understood.

We're one of the few centers that has an extensive experience on this. We have well over 20 years of experience longitudinally and hundreds of cases performed. And we have noticed a number of dramatic changes in the way that we are able to safely treat these patients. So today, we'll have a general overview of pediatric Neurosurgery in the skull base. We'll talk about some trends over time. And then, we'll focus on two areas of specific specialty here. One is early childhood surgery before the age of six and then patients with pediatric chordomas, which we are the center of excellence for.

So overall, over the last 20 plus years, we've had more than 250 unique patients and over 350 cases. You can see that, early on in our experience, we had a very high surge of cases. Let me just see if I can get the pointer. Here we go. So high surge of cases-- this really reflected us as the pioneers of this technique in children, getting a very large number of new patient referrals annually.

And then, there was kind of a slight drag where our technique was being disseminated to other institutions. And we've slowly and continued to have a resurgence with a formal person in the presence of myself being here and actively looking to expand the indications for skull base surgery and endonasal surgery in general. So we're really now back up to the 20 to 25 range of our peak in the early 2000's.

So looking at the age distribution, before puberty, there's a fairly stable distribution. We have children as old as just a few months old, and then, it really peaks around puberty. This, of course, is due to one specific condition called juvenile nasopharyngeal angiofibromas, which are strongly associated with pubertal males. And that is also the explanation for a slight male predominance in the endonasal exposure or the endonasal experience. But overall, most of these diseases are not gender specific.

So in terms of where in the skull base we operate, we divide the skull base into four distinct modules. We have the anterior fossa, the middle fossa, the posterior fossa, and the sella. And then, we also have what is called the coronal plane, which is everything to the sides and in front of these other modules, including the middle fossa so, basically, this one.

Overall, we have very nice experience in all four planes with a slight predominance of sella and coronal planes. And again, this has to do with the preponderance of juvenile nasopharyngeal angiofibromas and then also just sellar tumors like craniopharyngiomas, which are staples of the neurosurgical pathology list in children and also some of the earliest targets for our experience endonasally.

Over time, we see that our percentage of sellar/suprasellar lesions has decreased, whereas posterior fossa lesions has increased. And again, this reflects the gradual dissemination of this technique to other centers who may feel comfortable doing something like a craniopharyngioma, but perhaps not as comfortable accessing the posterior fossa and taking out a big tumor like a chordoma And then JNAs, being the majority of our coronal plane, have continued to be a mainstay all the way through our experience.

So looking at trends as a kind of suggested or chordoma experience, which is the primary posterior fossa, tumor access through the endonasal approach has dramatically increased over time. Adenomas, which are fairly straightforward tumors, has declined. Rathke's cleft cyst and other very straightforward tumor of the sella has declined. And our craniopharyngioma population has bounced around. Not entirely clear which way that one is going. And I think that reflects the fact that many of these come to us for redo surgery.

So looking at tumor trends-- so the size of the tumors that we've been treating has gradually increased to double our initial mean. So we have a mean volume now of 43 CC's, whereas, when we first started out, we were treating much smaller tumors at 22. And you can see that the number of large and giant tumors has really expanded, whereas most of the tumors we were treating previously were fairly close to this mean.

And again, looking at the complexity of the tumors, the number of tumors that don't invade into the brain, so extradural tumors, we've slowly seen that decrease. And the frequency of tumors that do have intracranial intradural involvement has gone up, again, reflecting the fact that the smaller centers out there are probably taking some of these tumors out but, again, don't have the expertise or experience to really tackle the more complex tumors.

Importantly, the preoperative level of cranial nerve palsies has gone up. And again, this reflects bigger tumors, sicker patients being referred to us for our very unique experience in treating them. So in terms of sphenoidal development, this is a major consideration for a lot of centers in terms of whether or not they would recommend an endonasal or transnasal approach.

So for our non-ENT colleagues, there are basically four stages of sphenoidal sinus development. The first is conchal, where there's essentially no sphenoid sinus. Then, there's a gradual expansion to what we call presellar, meaning that there's some sphenoid sinus, but it doesn't reach the sella. A sellar one that you start to shell out the front of the sella, but the clivus is not pneumatized. And then, postsellar, you have this large pneumatization that goes underneath the sella by at least 50%.

So here's just some examples. So here's a patient with conchal-- really doesn't have a sphenoid at all. Presellar-- there's definitely a sphenoid there, but there's a big wall of bone in front of the sella, in front of the pituitary gland. Sellar-- we're starting to carve out the pituitary gland but, still, the clivus is uninvolved. And then postsellar, we can see the pituitary gland is now nicely pneumatized all the way circumferentially except for above and behind.

So this is very age dependent. So the vast majority of patients before the age of six-- up to the age of six are either presellar or conchal, so two-thirds. So very few have real pneumatization. And immediately after the age of six, we see a dramatic change where almost everyone is at least sellar or all the way postsellar. And by the time they are in late adolescence and teenage years, they're almost entirely postsellar with about a third still being sellar and almost nobody being less pneumatized.

So that's very relevant because, like I said, that is often a major contraindication that other centers who feel that the lack of pneumatization makes endonasal surgery unsafe. That is not our feeling here. This is an example of a patient who has craniometaphyseal dysplasia. And you can see they, essentially, have hyperostosis of their entire sinus. There's really no nasal pharynx at all. Patient is a dependent mouth breather.

And this is an example of-- this patient specifically needed their optic nerves decompressed. I'll show that subsequently. But you can see, after the surgery, we've been able to very successfully and safely drill out all of that bone, reach the pituitary gland, reach the optic nerves. It can be done. It can be done safely. And it does require a high-level experience.

So here's just an axial view, again, showing here's those optic nerves. This one is essentially completely obliterated. And now, you can see the optic nerves are nice and widely expanded. And we've made the patient a very large space for their nose. So here's that video. Let me just turn off my pointer. So we looked at those pictures.

So the key to a case like this and to do it safely, you have to make your landmarks. There are no landmarks, but the landmarks still exist. They're just completely obscured at the time. So here we are creating a cavity for us to work in by mobilizing the turbinates. See, they're also ossified. And basically, you want to be constantly using your adjuvants like image guidance to make sure that you're not getting lost.

But basically, what you do is you make yourself a working space inside the center of the sphenoid, which allows you then to access the lateral borders. And then, what we do is we identify those lateral borders. We identify the periorbita, and we use the periorbita as a landmark to walk our way back. You can see there's the periorbita being manipulated. That was the bone above it.

So we can follow that all the way back to the optic canal, which you can start to visualize comes across here. And that allows us to create landmarks. So we do that bilaterally. And then, once we've done that, we now have the periorbita over here, periorbita over here. We can now start working to expose the sella and the pituitary gland to help us with their anatomy. So this is just an anatomy dissection I did during fellowship.

So here's the orbital contents. The annulus of Zinn is right here. So the optic nerve comes into that orbital contents, which we are following back. And then, you can use that to get all the way to the optic chiasm and across. And it also gives you a good sense of where the carotid is.

So now that we know this is our plane along here, we can dissect out that sphenoid here. And we know the carotids are going to be hiding right here on this adjacent bone, which we can then expose after we've found that true midline, which allows us, then, to complete the exposure of the optic nerves. So you can see there, there's the optic nerves right there.

So now, we can see here the optic nerves have been exposed. The dura is a little bit ratty, which is not unsurprising for the level of dissection exposure. So we just cover up some of that disturbed dura with a little bit of nasal tissue just to help it grow. But the patient did fantastic. He had improved vision. And I continue to follow him for recurrence of this condition, which unfortunately is progressive. So that's not his last surgery.

So, again, to summarize the way that you can do endonasal surgery in children without these landmarks is you want to be very comfortable creating your own landmarks. So pediatric bone has an enormous amount of lamellar bone, which is very soft. And so you're able to really drill fairly aggressively straight down to the inner cortex.

And you can kind of glide along that as I'm doing here. And this allows you to create those landmarks because those landmarks will be visible within the inner cortex. And then, you can get your midline exposure and then gradually lateralize it. So those are the carotid arteries that I'm exposing right here. So that's just some bleeding from the cavernous sinus. But there's the carotid artery here. There's the carotid artery there.

And this now looks very much almost exactly like an adult exposure. If you took a picture of this and asked a skull-based surgeon to age the patient, they would not be able to guess accurately between a young person and adult. This is exactly what it looks like in an adult. It takes a little bit more patience, a little bit more technique, and a lot more drill bits. But it is achievable, and it is achievable in a safe and repetitive fashion.

So there's a lot of studies out there that basically discuss the anatomic limitations in pediatric neurosurgery. And truthfully, the only one that we have ever found to be relevant is the width of the nares-- the bony width-- and not the soft tissue width. And that really does tend to be a little bit smaller in children under the age of seven especially.

And that doesn't tend to affect your ability to get into the superior or inferior plane, so anterior, middle, and posterior fossas-- or excuse me, anterior sellar and posterior fossa-- but it does affect your ability to get laterally. And we have some workarounds that allow us to adjust for that.

In terms of inter-carotid distance, this one gets a lot of press, people saying these young kids, they don't have enough space between the carotids to work. And while it is true in our data, as well as many other papers that the inter-carotid distance is age dependent, I actually do not think that this is a relevant consideration because, ultimately, it's the tumor's relationship to the arteries, not the distance between them that determines if you can take out this tumor.

So to continue, the inter-carotid distance is not really relevant. It's whether or not the tumor is medial or lateral. And if the tumor is completely medial, whether this is a small or big distance, really won't affect your ability to resect. Now, it may increase the likelihood that you need to expose the carotids. But again, at a center like this, that's something we're very comfortable doing. And so it doesn't really affect the ability for us to intervene upon these patients.

So in terms of getting more laterally, as I said, in these very young patients, it can be difficult to get so far lateral. And so we use supplemental approaches, such as transorbital approaches or anterior transmaxillary approaches. And that allows us to get that little bit of lateral extent that perhaps is a little bit harder in a young patient. So here, you can see we're taking this osteosarcoma off. It extended medially-- or excuse me, laterally into the orbit. And we were able to connect that with the endonasal compartment.

So that being said, overall, our ability to do these with endonasal approaches alone has been almost exclusive. There's always a few tumors that are too big or have other considerations where you need to do a craniotomy. Or maybe they have an unstable spine, and they need a spine fusion. Or it goes down into the neck, and they need a neck surgery as well. But the vast majority, almost 100%, are able to be done with just endonasal surgery and get excellent results.

So the reason why it's important to have a center such as ours is children are not small adults. Pediatric anesthesiologists are not small pediatric neurosurgeons. And it can be very challenging at a pediatric institution, no matter how polite and kindly we as neurosurgeons try to inform people, it can be very difficult to get the resources available to brace for judgment day.

And that is because this is such a rare condition. Most centers, you may do one or two or none of these at all. And this is really the kind of thing that benefits from a center such as ours that has experience doing dozens of these in a year because the resources that one might have in an adult skull-based practice are not going to be guaranteed at a pediatric institution.

They may not be used to the level of blood loss. They may not be used to the length. And they certainly aren't going to be used to the consequences and complications related to skull base surgery.

So even at a center such as ours, we've had a number of times where we've had to stop during surgery. So we've had to stage the endonasal case-- about 20 in total of 250 that we've done without any other approach. And I find the reasons very interesting.

So unsurprisingly, the most common reason that we have to stage an endonasal surgery is blood loss. And we'll get a little bit more into that in the next few slides. The second is there were five patients where we had residual that we thought we could get, and we went back for stage surgery. Two, the diagnosis that we got based on the initial pathology made us decide, rather than a biopsy, they needed a complete resection. One, we just had equipment failure and simply could not proceed.

One, the length of the surgery was so prolonged that there were concerns related to the patient's tolerance. And one time we had a case where we opened up, and we had profound occult sinusitis, which is, a risk because, often, we are not scoping these patients in the clinic because they're very young. And they may not be getting scans immediately before surgery because they have to be sedated, and it has to be done in a prolonged fashion some time before the surgical date.

So in terms of blood loss, ultimately, we're not typically operating on neonates. Usually, most skull based patients are at least a year old. So we really are looking at blood volumes of infants and children's typically. And our general rule is, if the blood loss exceeds about 50% of their estimated weight-based blood volume even with transfusion, that's when it's time to stop, obviously, redose antibiotics, and give the patient some time to recuperate before returning to the OR.

In terms of the going back because we saw residual, in three of the five cases, we were able to successfully remove the residual. And the patients subsequently have not recurred. In one case, we were not successful, and they got radiation. And they have not had any recurrence since. And then once, we were able to get the residual, but they did recur. And I think this is very important and useful information.

Specifically in three out of five cases, we were able to make a meaningful difference in the patient's outcome by going back in and getting a gross total resection. And while it can be challenging to harness the materials necessary to do these complex surgeries and to find the time to do another all day surgery, potentially, it really can make a meaningful difference in the children's life.

So looking at our outcomes-- overall, our outcomes are fairly similar to our adult population with overall about a 75% gross total resection rate in tumors endonasally. The remaining are essentially all near total, meaning 95% or more. And those that were subtotal were just biopsies. And the intent, ultimately, was not to get a gross total resection.

The most common near total resections that we deal with are craniopharyngiomas. This is because they often are adherent to the optic nerves, carotids, and pituitary apparatus. And so leaving some residual in order to avoid deficits or pituitary dysfunction is a major consideration in the treatment of these patients. Juvenile nasopharyngeal angiofibromas-- they are very invasive into the bone. It can be hard to catch the little nests, though we do try to drill out all the bone that we can.

And sometimes, they tend to have little fingers that go into very awkward to reach locations. It is a common problem. Sometimes, we go back for those. But depending on how close they are to the end of puberty, these tumors do typically stabilize or regress after puberty. And so if they're not having symptoms, we do watch a few patients with a small amount of residual.

And then chordomas, these are aggressive, malignant tumors. And they often are invading into bone that simply is in a position that cannot be resected, even with combined approaches, which we frequently do in this patient population.

So looking at our outcomes over time, again, like our other improvements, we have gotten better over time. And while our tumors have gotten bigger and more complex, not only has our rate of gross total been stable, if anything, it has non-statistically improved over time.

Part of this has to be credited to the fact that we have continued to add new treatments to our armamentarium. Two of our favorites are the transmaxillary approach, where we make a small incision in the gum line and make a small window in the bone up there through a Caldwell-Luc incision approach, which allows us to reach very far laterally even in young children.

And then, the other one is preoperative embolization. Again, the most common reason for staged pediatric neurosurgery is blood loss. So preoperative embolization for large tumors and vascular tumors or other vascular lesions is very helpful.

In terms of non-tumor pathology, again, 200 of these cases basically where tumors. The rest was a hodgepodge of things such as CSF leaks, encephaloceles, congenital anomalies, spine conditions like basilar invagination, and other miscellaneous things. One condition that I find very fascinating that is unique to the pediatric population and really seems unique to the female pediatric population is shallow sella syndrome.

And this is when congenitally, even if the patient is pneumatized, their sella is unnaturally undescended. And that isn't typically an issue until puberty, especially female puberty, where we see a tremendous expansion of the pituitary gland as it hypertrophies. And that can cause compression on the optic nerves and chiasm. The vast majority of these patients can be observed with just close ophthalmologic follow up.

But anyone who presents with papilledema or an optic nerve injury or field cut, simply by drilling out the bone here, that causes the sella to descend. And you can very easily prevent that from getting worse and usually improve it. Like I said, though, the vast majority don't need surgery. They can just be watched.

The compression itself is not an indication, in my opinion, for surgery, only the presence of a neurological deficit. As far as tumor types go, as we talked about earlier, JNAs really are one of our mainstays. And then, other common tumors that we see-- craniopharyngioma chordoma, adenoma, Rathke's cleft cyst.

As far as our complications go, by far and away, the most common complication that we deal with in skull based surgery is CSF leak in adult and pediatric. The problem is, unlike an open cranial approach, it's very difficult to get a watertight closure. You really can't sew the dura close the way that we do in open surgeries in most cases. So you rely upon multi-layered, vascular closures to try to get it to heal, as well as other adjuvants, such as external ventricular drains or lumbar drains.

We've gotten better with this. But this is without a doubt the primary risk and consideration for doing an open versus a endonasal approach in both adults and pediatrics. In terms of vascular injuries, we've had 4 over the 250 patients. One was unrelated to the surgery itself. It was actually a neck injury during a second stage transcervical approach.

One of the three was a direct carotid injury during surgery. And the other two were tears of branching vessels involved with tumors. We had three hemorrhages. Two of those were tumor bed hemorrhages, and one was an epidural hemorrhage from pinning. And we had three infections, all related to CSF leaks.

So in terms of our CSF leak rate, overall, it's eight. But if we are being fair and only counting large intraoperative leaks, what we call high flow leaks, the rate is as high as 20%, though, as we'll see, a lot of that is historical in nature. Unsurprisingly, the biggest cause of our CSF leaks are chordomas. The posterior fossa is notoriously hard to create a seal over. It is very far away from all of our other cranial pieces that we can potentially rotate. And it does represent the highest risk of leak in both adults and children.

An important point of the three infections we got is that they were all polymicro organismal on culture. And again, some of these may just be incidental flora. But I think it emphasizes that, if you are seeing someone who has a CSF leak that presents with a fever, you really should use broad spectrum antibiotics, including antifungals, until you have a clear source and a clear organism.

So in terms of what we've been doing to try to improve our CSF leak rate and that has changed is we've gotten much more aggressive with using multi-layer closures. So our use of grafts, such as free mucosal grafts, fascia lata graphs has gotten bigger. Our use of vascularized flaps, such as nasoseptal flaps, has gotten dramatically more frequent. And our use of CSF drainage has also gone up to try to supplement these closures.

As far as other outcomes go, in terms of cranial nerve function including vision, we're quite good of at least not causing harm and having stability of preoperative palsies. But we have a very high rate, about 50% rate, of getting improvement and a very low rate of causing worsening neurological deficit.

Pituitary function is a different story. Unfortunately, many of our patients are already panhypopit, and we can't really improve that. And we have a very high rate of patients getting worse of those that presented with some impairment already. And again, this goes back to really one specific pathology, which is craniopharyngiomas. It has been my experience that craniopharyngiomas in children, unlike adults, almost exclusively, come from the pituitary stalk, and they blow it out.

And so it's very hard to spare the stalk, which you can see right here, during surgery. We always try to. And we always make a conscious decision whether or not to sacrifice the stalk if needed. And it really comes down to a patient by patient consideration. Someone who is almost at puberty or in puberty might benefit from leaving a little residual and radiating to get them through a natural puberty, whereas someone who's already post-pubertal or who has many years before they even start puberty is unlikely going to get as much benefit because this tumor will, especially in the case of the patients who are prepubertal by many years, it's going to continue to grow.

And even if you use adjuvant radiotherapy, it's going to cause panhypopituitarism. But again, as I said, we always do try to preserve the stalk. This is our proof of that we have, at least in one case, not sacrificed the stalk at pit, which we are known to be quite aggressive about that.

And again, it's a balance because craniopharyngiomas have a greater than 33% recurrence rate. If you can get a gross total resection on your first case, that's their best chance of not recurring. It's very unlikely that, if you didn't get a gross total on the first surgery that you're going to get a gross total on a recurrence.

And so we really do try to balance the fact that patients with subtotal resection, they're going to have recurrence. They're going to have panhypopit from the radiation. And they may also get DI from subsequent surgeries and treatments. But it is something to bear in mind that patients who have radiosurgery and subtotal resection do have a lower rate of DI than obviously someone who has a stalk sacrifice is going to absolutely have DI.

And diabetes insipidus of the hormone dysfunctions, in my experience, the one that is most harmful and most deleterious to patient quality of life. So it is a acknowledgeable fact that patients, in some cases, may benefit from subtotal resection and Gamma Knife if it means sparing them DI.

So now circling back to patients who are very young, we have the largest experience in the literature in these patients under the age of seven. We've done, at this point, over 40 to 45. And just like our cohort as a whole, the diagnoses are quite variable, though there are a few that are most common. And our location is also quite variable. As we talked about, coronal plane is the hardest in these. So we have a little bit less experience, but we do have experience nonetheless.

So looking at how young children differ from older children, so interestingly, craniopharyngiomas in the pediatric population, even though they do have a bimodal pediatric and adult distribution in pediatrics, the vast majority of our center present young. Very few are post-pubertal at the time of presentation.

Encephalocele, unsurprisingly as a congenital anomaly, are very common early in life and are mostly traumatic or infectious in nature later in life. Epidermoid from nasal pits are also something that we see mostly in life. But then, we have these recurrences where they had a nasal pit and then, many years later, a dermal sinus tract continued to develop and create an intracranial dermoid.

JNAs-- again, they are basically a disease of pubertal males, really doesn't exist in this population. And similarly, adenomas-- very unlikely for a child to have an adenoma that has grown until much later in childhood, as are Rathke's cleft cysts. And I do think this is because both of these have a very strong hormonally-mediated drive.

So compared to our older pediatric patients, there is a lower gross total resection rate. And again, that comes down to these lateral borders that can be very difficult to get out so laterally through a very small nasal aperture. But it can be done as in this case.

These patients also represent a group that has the highest CSF leak rates. It was up to 15% early on. And this really has to do with a change in our own perception of reconstruction. Early on, we really didn't think that you could do a nasoseptal flap in a very young child, and we were proven wrong on this.

And we have subsequently changed our methodology to allow for extended nasoseptal flaps to take advantage of additional nasal tissue that's not actually part of the nasal septum itself in order to create better reconstructions. We've also gotten a lot more aggressive with using CSF diversion. And that has subjectively caused a dramatic decrease in our CSF leak rate.

As far as gross totals go, so craniopharyngiomas, as well as chordomas, have a fairly high rate of gross total resection even in young children. And again, this has to do with the fact that they are midline lesions. And they are amenable to the endonasal approach in early childhood provided that they don't go so far laterally that we're not able to reach.

And of importance, again, despite the fear that some of our other colleagues at other sites have about operating on early patients and the concern that the lack of anatomic landmarks makes it unsafe, we have not seen a significant difference in our complication rates. Specifically, we have not seen an increased rate of neurological deficit, visual, or cranial nerve. And we've not had any issues with vascular injuries.

Now, there is a trend towards worsened pituitary function. And again, this goes back to our preference to sacrifice the stalk if it means getting a gross total resection on a craniopharyngioma, which do make up about a third of the patients that we see for endonasal surgery in this young age group. They're so far away from puberty. Gross total resection is really their only potential chance of having a permanent surgical cure from this.

And so we are very aggressive except in situations where the tumor is adherent in such a way that it's not safe to resect, in which case we try to spare the stalk. And obviously, we do talk about this with the families, and we do give the families the option. Though sometimes, we're not able to follow through on that if the tumor has blown out the stalk. Sometimes, we don't even ever really see a stalk.

So in terms of recurrences, the vast majority of recurrences that we see in this age group are the craniopharyngiomas. Again, these are my least favorite tumors. Despite being benign, they are relentless tumors that cause immense morbidity in children and patients in general-- very challenging, especially recurrent ones. We've had two deaths in this age group, and these were both due to malignant tumor progression.

So in terms of recurrences, they're both in an older children as well as younger children. There does seem to be a trend towards greater recurrence-- non-statistical. But we are talking about very small numbers of patients.

And conversely, chordomas seem to have a lower rate than adults, though we did see a slightly higher rate in our young children versus our older children. And ultimately, both of these could be related to tumor-specific factors, the potential for growth and the level of growth factors in the body, or they may just be because we can't reach quite as far laterally. And so we're leaving small residuals that we can't detect.

So ultimately, though, chordomas are really the poster child for endonasal surgery as a midline lesion. It's possible to get an amazing resection in many of these cases. It's very tricky and, of course, a lot of experience and diligence because these tumors are right over the basilar artery, which you can see here. That's really not something that you want to mess with. But we were able to get it in this patient, specifically, we were able to get excellent margin, both dermal and bony. And often these tumors are cured by surgery alone.

So we initially thought in the pediatric or-- the initial assumption in the pediatric world was that chordomas have a worse outcome in children than adults. And that really was based on the open cranial literature. Open cranial approaches to the posterior fossa in children are extraordinarily challenging with very high rates of vascular and neurologic injury.

Since starting to do these endonasal, we've actually found the opposite that children actually often do better than their adult equivalents. And so what we have specifically found is that the overall progression-free survival using endonasal resection is about 80%. And very interestingly, it really stabilizes at three years.

And again, these chordomas are slow, relentless tumors. And I think if they're going to recur, they're going to recur quickly. And really, if they don't recur quickly, they're probably never going to recur, which is great information. And it really informs how we follow these in a staggered fashion with gradually increasing intervals of scans. But the first three years are really what makes or breaks.

Interestingly, we haven't had a huge difference in our outcomes between gross total and near total. And this is likely because of aggressive use of radiation therapy to back up a near total resection. We have not seen a difference between patients who presented to us for primary resection versus referrals for recurrent tumors.

And again, this reflects our unique experience to very aggressively and very widely exposed and resect these tumors, which is just not a skill set that a lot of other centers have cultivated to the same degree. And so having definitive resection by a center with a lot of experience really does allow even a patient with recurrence to benefit from that 80% survival rate. Radiation, as we talked about, can be very helpful. And we have seen a trend in outcome improvement with selective radiation use.

So de-differentiation is a notoriously problematic feature of chordomas, where they become the equivalent of anaplastic or glioblastoma. And they're extraordinarily aggressive. And we really don't know why they differentiate because they'll have a more benign type of chordoma. And then on recurrence, suddenly, we see this de-differentiation. And it's not clear-- did we just miss on the pathology that the patient had already differentiated, or is this a novel change that occurred after the initial resection?

So looking at our four patients who did de-differentiate, two of them had treatment prior to resection, meaning that the full bulk of the tumor got radiation. And also, two of those patients had a Ki-67 on initial resection of 15% or greater. And this makes some level of sense, which is that, if you radiate more cells and those cells have a higher replication rate, the potential for that radiation to induce di-differentiation mutations is likely higher.

Of note, the only two patients that we had nasal seeding, which is a form of metastasis where the chordoma, goes along the resection tract, have also only been in patients with de-differentiation. We've seen a dramatic reduction overall in our adult and pediatric populations with this issue by using silastic sheaths in the nasal cavity to prevent contact with the nasal tissues and the tumor that we resect.

So that's really all I have to say on the topic. I'm happy to answer some questions. And again, if anyone has referrals or other questions, they'd like to reach out to me, this is my email. Happy to chat.