Obviously there's been a very nice introduction to how we initially evaluate these patients and the medical treatment of some of these tumors and we're going to talk more now about some of the advances at least in pituitary surgery and treatment with radiosurgery.

So the initial, the indications for surgery I think have been covered pretty well by Heather and Dr. Brooks and Dr. Challinor, but basically the obvious indications are where there's optic compression in a nonfunctional tumor or a case where there's apoplexy with similar compression. More difficult cases are incidental adenomas without and with pituitary dysfunction, again things that Heather talked about and covered.

The traditional approach for pituitary tumors is the transsphenoidal approach using a microscope. There were two ways to do that one is sublabial under the line of the gum and the other is transseptal where an incision is made either in the front or the back of the nasal septum and a speculum put in place to allow the microscope light in. More recently over the past 10 years or so has been introduced the endoscopic endonasal approach which is using an endoscope in one or both nostrils. And there are a couple of different versions of that. One where people do a traditional transseptal approach with a microscope and then put a endoscope in at the end or a purely endoscopic approach.

The limitations to the microscopic transsphenoidal approach are largely a result of having to place a mechanical speculum into a place and deliver light down into a dark hole and so the areas that are limited are the areas beyond where the speculum immediately reaches. So the suprasellar area is

traditionally not accessible although it has been extended to the suprasellar area and most importantly the cavernous sinus really can't be well accessed through a microscopic approach, very, very wide sublabial approaches can sometimes access more lateral areas but it's just really not well visualized with a microscope.

This is just looking at the view you might get with a microscope even with a wide exposure is basically just the sella and whereas with an endoscope just with a single view you get all of this view, and this actually is a view with an endoscope and a cadaver. This is sort of a nice metaphor for understanding the difference and it's basically the difference using the same corridor but the difference in what you are using to visualize and deliver light. With a microscopy you can zoom in to get magnification of whatever you are looking at, but the endoscopy allows you to introduce it into the depths so that you can actually look through that window and get a much wider view. So the view that it gives you is significantly different, and this can allow us to access areas that simply couldn't be accessed before. So the endoscopic endonasal approach as we see it is a – it's a fully purely endoscopic approach, it's completely through the nose and the paranasal sinuses and it's a series of different modules to the entire ventral skull base and this was a technique that was largely developed here through collaboration between ear, nose and throat and neurosurgeon doctors and neurosurgeons.

The way we do it is with two, through two nostrils, we introduce the endoscope into the right nostril at basically the 12:00 o'clock position, place a suction or dissecting instrument below it and then

another dissecting instrument through the other nostril and the basically wide opening into the sinuses gives us full access to the skull base. We do this with an ear, nose and throat doctor and a neurosurgeon working simultaneously for the simple reason that we are working, we have different goals and different areas of expertise. As a neurosurgeon I'm looking to expose the pituitary widely, I want to see the critical things such as the carotid artery and optic nerves so as to not damage them and work safely around them and also to have working space so I can work with both my hands like I would with a traditional open surgery; whereas the otolaryngologist is trying to preserve the nasal anatomy and function at the same time as provide safe access.

There are things obviously that we look for that Bill talked about somewhat, again traditionally because there is not wide access if you have a patient who doesn't have a pneumatized sphenoid it's very difficult to see and safely remove this, but with modern image guidance and with using endoscope for the pneumatization pattern doesn't really matter. It can make things slightly more difficult but doesn't keep us from doing the surgery. We've had very high rates of preservation of olfaction, the rate is about 5% loss of olfaction; all patients lose olfaction perioperatively for 2 to 3 months because the air flow is disturbed we think but it returns to basically normal in all but about 5% of patients.

This is just showing the steps that we use in order to access the sphenoid and areas around it. I'm just going to show some of these steps. This is just a view with the endoscope initially looking in the nose and that's actually a normal ostium into the sphenoid sinus. So actually just directly entering

the nose we have very good access immediately back into the sphenoid sinus and then just opening up that sinus gives us good access. One of the initial problems was once you make this large hole how do you then close it back up and we've helped develop a technique also using part of the nasal septum as a flap to help prevent spinal fluid leak postoperatively. This is just showing that flap, basically it comes off the septum and can be placed anywhere on the skull base to prevent a spinal fluid leak. It's living tissue, it's still attached to its blood supply and provides very rapid healing.

This is now showing widening that access, there is that sphenoid ostium, we can simply open the ostium, remove all of the bone into the sphenoid. Now a typical microscopic approach would basically be to remove this amount of bone in the middle and that would be the full access that you are given; but with the endoscope we can see much more and in order to work with both hands in the same we would if this were an open approach we resect all of the bone and basically the entire front wall of the sphenoid sinus is removed and that gives us full access to this large adenoma here. And so in the end it's all about having this very wide exposure to the tumor. And we'll spend an equal amount of time exposing the tumor and exposing all of the anatomy as we will with tumor dissection and this really in some ways saves us time because it allows us a unique ability to do tumor dissection.

Just looking at some of the anatomy that we're able to access again a microscope gives us access to this point, but in this endoscopic view we can see this entire area that Bill talked about earlier from the planum sphenoidale which is far in front of the pituitary, the tuberculum, the actual sella itself,

the clivus below the sella and then the carotid and the optic nerves to see all of those structures around the sella that we could potentially harm. And this showing just that wide exposure that gives us full access, you can see we have room all around the tumor to work rather than opening just into the center of the tumor; one of the things that we'll do is the cavernous sinuses surround the pituitary and the sella, really it's called the circular sinus because there's a circle of venous sinus that's all around the pituitary and we like to expose that so that we have access to the soft tissues all around the gland into the areas it can invade, the tumor can invade.

So that's really one of the key differences here we are removing bone over the carotid artery because that's what allows us to get access to the cavernous sinus. Again we can see out over the carotid artery, we can safely drill and remove bone over the carotid artery and that allows us to access a tumor that's behind the carotid artery. This is one of the very unique things about doing pituitary surgery with an endoscope. With this large tumor once we have the exposure then we simply can open the dura, these are instruments that are sort of designed to allow us to do this in the same way we would if this were an open surgery, so we are using some of the same instruments just with modifications to allow us to use them through the nose.

This is a typical adenoma, they tend to be very soft like this. This is one of the reasons that a lot of times with a microscopic approach even with a smaller opening you can get a pretty nice removal because the tumors tend to be rather soft. But you are limited once you get a fibrous tumor or a tumor extending more laterally. One of the first steps we do then is to send some specimen off to

pathology as much as possible. This allows, obviously if we don't send enough specimen then can't do immunostaining and sometimes that can be one of the most critical components in determining patient postoperative function as well as even things such as recurrence. At the end once the tumor is removed we like to see the entire diaphragm distend into the opening that we've made with large tumors, then we know we've removed the entire tumor.

Without this large opening a lot of times we can't do an extracapsular dissection, pituitary tumors when they grow they grow from inside the gland in general and they compress the pituicytes around them and those compressed pituicytes form a pseudocapsule and that capsule itself can be dissected free from the gland. And if you can stay in that capsule you know you can remove all of the tumor because that gives you a nice border around the tumor. There are some cases like this, very fibrous tumor that's not very soft and you can imagine if you made this small opening into the tumor and tried to curette the tumor you simply wouldn't get an adequate removal. But because we have a very wide opening we are able to work around the capsule of this very fibrous tumor to remove the tumor basically in one piece. So this is essentially a typical microscopic opening but then because of this wide bony removal that we've done we are able to work around the tumor.

So here we'll see you know as Bill pointed out earlier the gland enhances much more than the tumor, and what we see here, this tumor has compressed the gland over the top under the diaphragma and the tumor itself is very pale and doesn't have much vasculature to it but the gland that's compressed against the diaphragma has this very fine reticulin pattern of vasculature and you can see just by

looking at this why the gland enhances more than the tumor does itself. You really see very nicely the distinction between the two, between tumor and gland. And here we are starting to see how, this is just that compressed capsule and here is where it's becoming probably part of gland. So by transecting that attachment then we leave the gland intact, compressed on the diaphragma and able to remove the tumor in this case in one piece because it's a fibrous tumor. Here is maybe the most difficult part with a large tumor and that's sometimes getting it out the nose if it's in one piece.

Here is the septum, you can see some of the mucosa has been removed in order to do a flap at the end, and that re-mucosalizes very nice on its own. Here is the postoperative MRI, you see the stalk and the gland which has been flattened and pancaked by the tumor growth but it's already coming back into a normal position, already is much thicker and here is that septal flap that Bill talked about that you see enhancing. There is the gland and stalk and there is the septal flap. So one of the other main surgical indications other than purely mass effect of a tumor is prefunctional tumors and for ACTH and growth hormone secreting tumors surgery really remains the primary treatment modality.

Here is an example of Cushing's disease and again we try to take – here is a small microadenoma, we try to take advantage of that capsule in order to make sure we get complete removal of the tumor. So here is the sella, we've exposed the right carotid artery, here is the pituitary gland covered with dura and the left carotid artery still has bone over it. The – you can already get a hint of where the tumor is with this bulge in the dura, and so we are simply opening the dura just to the midline side of the tumor, and you get a peek there at the whitish tumor, again compared to more yellowish or

vascular gland. And so by staying in this area of pseudocapsule we can work around the tumor and remove the tumor in one piece. And what's interesting to me is that you can see here the tumor really stays relatively adherent to the dura and this is why something like Cushing's disease really can recur. It doesn't take a very large recurrence to be symptomatic and if the tumor is just sort of debulked you may have tumor cells left behind in the dura that could then grow back in a few years. And that to me probably explains why we get recurrences. So we try to remove the majority of any involved tissue that we possibly can. So here we see nice preserved plane with the gland, here we see carotid artery, the tumor is still only just adherent to the dura as its last point of adherence. So we remove that dura along with the tumor.

Here we see the carotid artery, just some venous bleeding from the cavernous sinus which we can control just with some packing. You can see this wide exposure allows us to work with two instruments and allows us to really see the carotid artery and the cavernous sinus very nicely. And just removing some of those other tissues that were involved to make sure there is no microscopic tumor residual.

Here is her 2 years postoperatively, still in remission. So some of the advantages of the endoscope are the simple fact that we can see and work in the parasellar areas that you simply can't do with a microscope, and there is more and more data coming out and I'll show some even from our institution that really shows that this cavernous sinus extension can make a difference for some patients. Subarachnoid tumor extension, when the tumor breaks the diaphragma and really extends

in the subarachnoid space we can access that. For recurrent disease a lot of times disease has been left behind after a microscopic approach because it's a fibrous tumor or because it's invading the cavernous sinus. If that's the case we can then access that recurrent disease. And again we try to really put an emphasis on the microsurgical technique in order to preserve function and not do blind surgery essentially.

Here is an example of a patient with acromegaly and acromegaly is notoriously difficult to cure with surgical cure rates only somewhere around 40 or 50%, and a lot of times it's because tumors are very invasive. Here we see this tumor extending well into the cavernous sinus past the carotid artery here. And again with the endoscope we don't just have access to the sella but we do have access to the parasellar are including the cavernous sinus. So here is just removing some of the bone over this carotid artery in order to have access to that left sided cavernous sinus.

So here is once we are actually in the tumor, the bone again over this carotid artery has been removed and here is removing a typical whitish growth hormone secreting tumor. They tend to be even whiter and paler than other tumors. So here is the cavernous sinus wall now, there is normal gland being lifted up and here we are actually working in the cavernous sinus, you see some venous bleeding from the cavernous sinus that we'll control later with just packing. And here we are suctioning now working behind this carotid artery, because we've exposed the artery, removed the bone over it we can actually gently move the carotid artery over and work behind the artery in order to remove tumor within the cavernous sinus.

Here is a little better view of that same cavernous sinus after we've packed off some of the bleeding. You can actually see the medial cavernous sinus wall with maybe a little bit of tumor still adherent to it. Here is putting image guidance in showing how we're working in the very back wall of that cavernous sinus. And then one of the final steps that we'll do then for functional tumors is resect that cavernous sinus wall. Here we see the left carotid artery, we are working behind the artery. And this is the dura of the medial cavernous wall and we can remove that dura in order to make sure that any infiltrative tumor is removed along with it. This is just a stimulator to test for the extraocular movement nerves 3, 4 and 6 that Dr. Stefko talked about in order to make sure we don't damage those while removing tumor. So this is fully in the cavernous sinus which is traditionally an area that was considered to be not accessible surgically. There are still areas obviously where those nerves reside, if the tumor invades where the nerves reside it's again not resectable without unnecessary risk.

Here is a postoperative MRI of that patient showing a complete removal and he is fortunately still in remission. We do monitor the nerves for extraocular movement with small needles that are placed in the muscles for extraocular movement. Sometimes patients can get a little bit of periorbital hematoma just from that needle monitoring, but here you see this guy with normal eye movement postoperatively.

So in acromegaly there have been significant improvements in overall control rates because of adjuvant radiosurgery and also improvements in medical treatment but the primary treatment upfront does remain surgical; microsurgical remission rates range from 50 to 60% using modern criteria that Sue talked about but it depends on the degree of invasiveness. There is a wide range from 40 to 60% in surgical series depending on how much cavernous sinus invasion there is.

We looked at 42 patients who had endoscopic endonasal surgery for acromegaly over the last 10 years approximately and the degree of invasiveness was analyzed using a Hardy Classification, which I'll talk about in a little bit that classifies basically on how much the tumor invades above the sella and down in the sphenoid sinus or the Knosp Score that Bill showed which tells how much the tumor has grown past the carotid artery into the cavernous sinus.

So our criteria for disease control were normal IGF-1 levels and a suppression of growth hormone level to less than 1 nanogram per milliliter after glucose load or just a random level of less than 2.5 and a minimum of 3 months post-operably. So out of our patients 92% had macroadenomas so very few microadenomas in this series and a quarter of them were recurrent tumors who had a 3 year mean follow-up.

We had complete data for that full period of time for 35 patients, and of those 24 received only endonasal. We then followed up in patients with cavernous sinus residual with radiosurgery and we found that this combination controlled many of the patients and then further adding medical

treatment at that point. With just surgery alone, even with invasive and macroadenomas, we had disease control or remission or I hesitate to use the word cure, but disease control in 63% of patients. If you include the patients treated with other modalities including radiosurgery and medical treatment we were able to achieve control at 83% of the patients with pretty strict criteria for growth hormone control.

Now if you look at the Hardy Classification and basically split it down the middle between Grades A and B and Grades C and D, Grades C and D are those with significant invasion or suprasellar extension that makes them traditionally much more difficult to cure. Here is the case of an extremely invasive tumor extending into the lateral cavernous sinus up in the suprasellar space, even up toward the frontal and temporal lobe we had essentially 64% of our patients had some sort of highly invasive tumor like this, so more than half were more complex cases. And this is a great example of removing the majority of the tumor leaving intact gland but leaving tumor in the lateral cavernous sinus, but that's the portion where the cranial nerves are and again by treating then this residual with radiosurgery and adjuvant medical treatment we were able to control patients like this despite having very large invasive tumors.

Here is an example of a patient with a very invasive tumor. This would be a high Knosp Grade with tumor basically surrounding 360 degrees of the carotid artery, a very invasive tumor with suprasellar and sphenoid so a Hardy Grade C or D and extension here both of in front of and in back of the carotid artery in the cavernous sinus. Well because of the wide exposure we are able to resect the

tumor both in front of the carotid artery, which you see here, as well as back behind it. Now the only area we don't venture into is again on the superior lateral side of the carotid artery, this is the left artery. There is a small branch off of the artery that will coagulate, but that superior lateral side is where the nerves for extraocular movement are and because we get such good control rates with adjuvant radiosurgery we don't think the risk of potentially harming those and closing a patient's eye is worth that tradeoff of going after tumor in that area. But here we are able to access well around the carotid artery on both sides. Here we see tumor invading the cavernous sinus. There is actually the 6th nerve there running here, so this is sort of our stopping point. Once we get to start to see those nerves then we are within the cavernous sinus and then resecting tumor beyond that becomes too high risk and not worthwhile for the patient. But you can see how invasive this tumor is within the cavernous sinus, and this is one of the reasons that acromegaly can be so difficult to treat. But here we see the normal gland and then where tumor was resected from the cavernous sinus. Here is the postoperative MRI which you can see complete removal from this extended area of the cavernous sinus.

So when we look at purely Hardy Classification the cases that had low Hardy Stage, so these not these giant invasive tumors, we had a 92% remission rate with only surgery and 100% remission rate with surgery plus radiosurgery and adjuvant medical treatment. In the cases with a high Hardy Stage, as you would expect, we only had a 50% remission rate and also lower rates with combined therapy.

If you look at Knosp Score, so this is invasion basically higher grades of Knosp indicates invasion in the cavernous sinus. Even with cavernous sinus invasion we were able to achieve 60% remission in endonasal. So the cavernous sinus is not a – does not a contraindication for surgery and it's also an area that by using the endoscope we are now able to achieve some advance in our ability to control disease in that area. As you can see when the tumor is truly invasive like that it can be very difficult to remove all the microscopic disease safely and that's when these adjuvant treatments come into play. But cavernous sinus really is not been – not as much of a barrier as it used to be.

If you compare this to some traditional transsphenoidal microscopic case series, if you – here is an example of a large series that's really somewhat similar, their definition of invasiveness was a Hardy-Wilson 3 or 4 Grade. In those cases they had 28% invasive tumor, we had about 61% but very similar total remission rates. So it's not that we are able to cure some of these tumors that are still invasive and basically become a part of everything around the sella, but some of these more invasive tumors are much more accessible and that enables us to achieve still good remission rates despite higher invasiveness.

Some of the complications as you might expect we have – we do have one cranial nerve palsy, a 6 nerve palsy leading to double vision; endocrine deficits after all treatment, we had 7 patients with endocrine – with new deficit in one or more axis; 3 cases spinal fluid leak and 3 cases of meningitis. The visual outcomes in this series of acromegalics we had improvements in the visual field or acuity

from preoperative, deficits in two patients and we had no patient basically with permanent worsening of vision among the acromegalics or any pituitary for that matter.

So in conclusion for acromegaly anyway what we found was that the endoscope allows us to gain better access to some of these invasive tumors. It's still by no means is it a cure all, but combined with radiosurgery and medical management we do provide I think a very high rate of disease control with low complication rates.

Supra – so what about suprasellar extension, extension into areas other than the cavernous sinus? One of the other indications for surgery is medication resistant prolactinoma. This is an interesting picture I found in a castle in Europe actually. This is a case of suprasellar prolactinoma. This is a woman who is already I think on 3 mg a week of Cabergoline in relatively high dose and has – the tumor has shrunk somewhat, probably about 20% but she's interested in becoming pregnant and there is obvious at least contact with the chiasm, she does not have a visual field deficit but her obstetrician was very uncomfortable with her coming off of the Cabergoline to go through pregnancy and so this is someone who now we have to consider for surgery despite this suprasellar extension.

This is a case actually that Juan did and this is just again looking at the sella, we have a nice white exposure here in order to see the areas around such as the carotid artery, there is a little bit of cavernous sinus invasion with that tumor in addition to the suprasellar extension and so all the bone over the carotid has been removed really on both sides to have wide access. And you can see the

bone in the suprasellar area above the sella here has been removed to give us access. So here the dura is being opened and we start to see the outline between the normal gland and the tumor here. And these tumors whether it's because the ones that are more resistant are fibrous or because the treatment makes them more fibrous we do find that prolactinomas that have failed medical treatment do tend to be a bit more fibrous.

And so here – you see this sort of extracapsular dissection, it's not a nice soft suckable tumor, but here is that plane between the normal gland and the tumor. And so this part toward the cavernous sinus now has been removed and here working in the cavernous sinus. So you see again a very fibrous tumor, it's a little bit invaded that cavernous sinus wall and so by working behind the carotid artery here we can really make sure we remove all of that tumor within the cavernous sinus. And here we start to see a much more cavernous sinus wall. But now there is still that suprasellar portion of the tumor that has to be addressed. The sort of venous bleeding, actually we have some nice materials just to pack it off, it's never a major issue.

We've talked about cavernous sinus a bit so I'll fast-forward through this part. But the next step then after really dissecting all of this part is the suprasellar extension which is really the key for her is to get the tumor away from her optic chiasm. And in this case a very fibrous tumor that's not necessarily the easiest thing to do, he is just resecting some of the other. So now we are working up next to the pituitary gland into the suprasellar space. The tumor has invaded through the diaphragma, here we can actually see the diaphragma, the opening in the dura and here is that very fibrous tumor

being teased away from the gland. Now obviously this case was very delicate, in addition because this is a woman who is looking to bear children and so we want to make sure to preserve her hormone function. So a careful dissection here is critical, we can't just reach up and blindly pull out the tumor. And what we'll see here is that the tumor is very much – you see these adhesions here to the pituitary stalk. And so just by cutting those adhesions sharply we make sure not to damage the stalk and potentially damage her function or ability to have children in the future. You see it's a very fibrous tumor, it can't just be suctioned out, it really has to be cut up and removed in pieces and carefully dissected that way.

Here we are looking up into the suprasellar space there, you see the pituitary stalk nicely preserved. Here is the gland, the pituitary stalk and we are right on the back side of the optic chiasm and we can see this is just some arachnoid. You can see that area where the tumor was touching the chiasm there, it even caused some indentation, a little bit of bruising of the chiasm that it seems to have tolerated. I always find it fascinating how much the tumor can grossly impact on the chiasm. And here is the postoperative MRI showing complete removal and as she's – you know I don't know if she has been able to get pregnant or not, I don't remember but she has had recurrence of her periods.

Here is an even more invasive tumor extending up into the third ventricle, a similar kind of idea where again because of the endoscope we can really access tumor that couldn't be traditionally accessed. Here is the postoperative, immediate postoperative MRI with complete removal of all but

a very small portion of tumor up in the third ventricle and here we see the gland sort of off to the side, I think that's it right there.

So when we open in the ventricle or in these fluid spaces what we've found by extending these approaches that we had much higher rates of spinal fluid leak because we were accessing tumor that wasn't accessed before and so we started using this nasal septal flap for about the last 5 years which has greatly decreased our spinal fluid leak rates to about 5%.

This is just showing our continuum of patient care really consists of the entire team of ENT and neurosurgery seeing the patient at different time periods both before and after surgery with different roles that continue to complement each other. They basically – all the patients stay on antibiotics for a few days while they have some nasal packing in place if there is a spinal fluid leak, there is no packing if no spinal fluid leak and essentially have nasal irrigations for about 1 to 2 months typically postoperatively. There are nasal complications associated with this where you can get small abrasions or burns from our instruments. There is always a transient anosmia and they get nasal crusting obviously while they are healing.

So about major complications, the carotid artery injury rate in the literature is somewhere around 1 to 1.2%, as high as 1.4% with a traditional microscopic transsphenoidal approach. With endonasal surgery despite working around the carotid on a regular basis, working in the cavernous sinus we

only have an injury rate of .3%, we have not had a stroke fortunately from either of those injuries. Here is an example of one of them. We've been able to control the injuries intraoperatively.

Other postoperative problems, more minor, things such as nasal crusting, olfactory loss and spinal fluid leak as I talked about overall with all cases for intradural surgery even things like cranial pharyngismus and meningiomas, when we looked at 150 cases done with the flap when we first started using the flap there was only a 4% postoperative CSF leak rate.

So in conclusion I do think that the endoscopic approach provides a much wider access and that gives us access to the cavernous sinus and the suprasellar and even intrasellar spaces that we simply didn't have before with a microscope and this I think is most notable when we start addressing functional tumors. We are hopeful that this will also lead to long term more evidence of lower recurrence rate in nonfunctional tumors and a decreased complication profile has been shown in the literature. Thank you very much.