

So now we are going to give you some data from our endocrine active tumors, this isn't as beautiful perhaps because of the difficulty of these tumors and why combination treatment is extremely important and I'm very grateful for Dr. Liu who helped put together this data.

So we talked a little bit about the nonfunctional tumors for trying to attain tumor growth control, preserve function, preserve existing endocrine function and eliminate some of the long term risks of radiation therapy. But there are two other important factors related to hormone active tumors that we have to consider. One is we need to try to get rid of this excess hormone secretion, or at the very least we'd like to reduce or eliminate the use of suppressive medications that cause, as I'm sure you've heard, the very long term costs of this.

And we should remember that this is a single procedure done in a single day, it's based on a frame application, this is a guiding device for stereotactic frame, every patient comes in the morning, we give them a little bit of a relaxation technique, we use local anesthetic and we attach this guiding device to the head and then we go over and do an MRI scan and then we bring the patient back. We do a computer plan, we do the treatment and the patient goes home in the same day. In the older days when the planning systems were a little bit slower the patient could sit there and read the New York Times while we did the planning and then we'd do the treatment. Now we often treat 5 patients in a morning, we can – we start early in the morning putting the frames on, we get the patient's image with MRI scan by about 7:00 or 8:00 o'clock in the morning before the radiologists wake up, and that way we don't have any problem to get the imaging that we need. We are there supervising the type of imaging that is being done. We don't have to do an hour and a half MRI scan

on most of these patients, we are doing a scan which allows us to localize the target within the head and almost always it's being done with MRI. And that's because it's only with the MRI scan that we really can see the tumor.

So over the years there has been a lot of confusion about things and one of the reasons that Sue talked about is that as surgeons we always could be thought well we are doing a relatively good job and then every couple of years the endocrine teams would get together and change the rules. So they would say you know 25 years ago you know growth hormone less than 10 was great. So there were a lot of papers published in our literature saying well we've got all these patients with growth hormones less than 10. Then somebody said well, actually it needs to be less than 5. And then somebody said no, actually it needs to be less than 2.5 but you need to have it less than 1 when you do a glucose tolerance test and besides that the IGF1 that we cooked up, also that needs to be normal for age. And so the bar kept getting raised for this. And as you read the literature you got more and more confused because what happens, somebody was talking about one set of values and also the type of values that were being used weren't understandable from one place to another.

But one of the things that came out was that Alex Landolt is a great microsurgeon, done thousands of pituitary tumors and then started using gamma knife as a cleanup hitter, and started to think well, actually we found that it works much better and faster than radiosurgery but we are little worried that some of the suppression medications that are being used actually reduce the rate of response to gamma knife. So a sort of story emerged in our world which we actually think is probably not true, that patients on suppression medication don't do as well as patients who are off suppression

medication and that for patients like growth hormone secreting, most of whom are now on Cabergoline, they need to be off the suppression medication before you do gamma knife and the same for patients with Prolactin on Cabergoline or growth hormone patients on Sandostatin, so it turns out at least in our data that those, usage of those agents on or off medication does not affect the results. So what we need to do to achieve the goal is we have to give much higher dosages because here we are not only trying to stop the tumor from growing, inactivate the tumor, but we actually want to shut down the biochemical protein synthesis of the cell. And that requires a much higher dose in order to achieve that, that effect.

So if we look at growth hormone and we are trying to achieve this particular high benchmark growth hormone values less than 1 and the glucose tolerance test with a normal IGF1 and we have to get the normal pituitary profile. So here's a typical patient with a growth hormone secreting residual tumor that's out lateral on this particular patient and after a period of time a significant reduction in this particular tumor, which is not an overnight effect, it may take many months or even years before we get that type of response. Here is another patient with this type of tumor with a smaller tumor over the course of time in about 3 years.

So 58 patients we've looked at now with clinically active acromegaly, we lost 11 patients to follow-up and we excluded 4 patients who had less than 2 year follow-up, more women than men in this with a average age of about 40 or so. Most of these patients it is expected, they had prior surgical resection, a few had had surgery followed by radiation therapy, and the reasons to consider were not only residual tumor but also that these patients were resistant to suppression drug or simply couldn't

tolerate the drug, only one patient. And by the time they are treated 58% of these patients already have some form of pituitary axis loss, many of them have invasive tumors and we looked at this value of the IGF-1 index which is the value of the patient divided by the upper limit of normal for the patient, which is age and gender specific.

So again we started out with the various models of the gamma knife that we've used, we put on the frame, we do local anesthesia with sedation, the imaging is required and these are postoperative patients because as you've heard the gland enhanced more than the tumor does, we want to actually give a low dose of the contrast, about half of the dose of the usual dose of Gadolinium or other paramagnetic agent. And then we use a varied volume scan to be able to get sort of a 3-D picture of this and then new planning systems for this.

So the endocrine follow-up in these patients is now out over 6 years or so, we are using higher doses for this but we are keeping the dose to the optic nerve using gamma knife well below 8, 9, 10, which is actually well within the tolerance of these types of tumors. And we get these types of high resolution imaging, this is target based treatment, we do the treatment plan here as you see on the coronal and the lateral view with significant regression of this tumor over the course of time, and this page IGF-1 level is significantly better although not probably age normal for this 51 year old patient, but he is off of any suppression therapy at this time.

And if we look at the response rate for acromegaly we can see that tumor control that is prevention of tumor enlargement of further growth can be done in the vast majority of patients. And this either

means further shrinkage of the tumor, measurable eye imaging or that the tumor shows no further signs of growth with only one patient showing further growth. But that's the imaging result and from the endocrine perspective what's more important of course is what happens to these patients in terms of their endocrine activity.

So in this group of patients with residual recurrent tumors we could obtain remission defined as a growth hormone level less than 2.5 and a normal IGF-1 for age off of medication in about 44% of patients. And control was achieved in another group of patients but these patients remain on suppression medication over the course of time. A process that takes time to develop so that these patients can't be told well it's going to be done in X number of months, or we're going to see it, we begin to see effects certainly in most patients within a couple of years but the overall effect will build up over time and so we can't sort of say that there is a single point in which the patient may or may not have responded to the, to the procedure.

If we look at the significant factors in a multivariate type of analysis we did not find that patients on suppression medications for acromegaly had any different outcome than the patients who were off suppression medication. And yet certainly if they required medication afterwards, suppression medication, those patients were going to do better with lower values. Tumor invasiveness as we might expect was an important aspect in terms of response and the more invasive the tumor the more difficult. Looking at the IGF-1 index before the procedure, if the index was less than 1.5 then the tumor, then the hormonal relapse rate was much, much better than if the patients had very high levels beforehand with much higher growth hormone and IGF-1 levels.

And similarly the response rate was much better for patients with less invasive adenomas compared to patients who had more invasive adenoma complications. No patient developed any optic nerve loss, our plans were always based on very specific sparing of optic nerve structures. No patient developed a new deficit of extraocular movement, no patient developed diabetes insipidus, but if we look at patients with the eventual development of at least one additional pituitary hormone axis this was seen in about a third of patients.

One new axis in 6 patients, 2 new axis deficiencies in 9 and 1 patients with since a pan hypopituitarism with those particular findings over the course of time. When does it occur? It occurs anywhere from 9 to 145 months after the procedure, but on median about 3 years after the procedure.

Did they need something else done? Not very many. One patient had repeat surgical resection, four patients had repeat radiosurgery for evidence of tumor growth. And if we look at other reports of gamma knife for these types of tumors we see similar rates of new hypopituitarism in about 1 out of 3 patients over the course of time.

So for these patients with acromegaly we think it's effective in many patients for these residual or recurrent tumors and think it should probably be done early in the patients who have this particular disorder because of the lifelong risks related to excessive growth hormone hypersecretion so we don't think that these patients we should wait.

Prolactinomas are an even greater challenge, Paul has talked about that. And the reason they are because of the reasons we end up treating a patient is because they are very invasive, number one, and because other treatment has already failed, because clearly the initial management of these patients is medical with suppression, suppression therapy. And it's being used in these group of patients who have generally failed that. In our series of 22 patients with tumors that are laterally invasive in the cavernous sinus interesting male and female about the aside, all of these patients have had medical treatment or radiation therapy and 15 had had prior surgical resection. So 13 of these patients had resistance to suppression medication or 6 who had had intolerance of it, and 8 of these patients already had some form of endocrine loss after the initial management of the patients.

The same way that we do these patients with the gamma knife treatment as we talked about, and tumor volumes, larger tumor volumes which require some lowering of the dose to preserve optic nerve function is going to be necessary in these invasive types of tumors that are larger. But a typical finding might be this 62 year old patient with a residual left cavernous sinus prolactinoma, serum prolactin level was 258, on Cabergoline and 22 months later there is significant tumor shrinkage, the prolactin level has now gone down to better, not normal. So if we look at this we can see prevention of tumor growth in most patients, however or regression, but 3 patients had delayed tumor growth over the course of time and if we look at variables in this relatively small series, age was important in looking at the sort of response rate. The younger does better.

What happens to the endocrine outcomes? Well in terms of complete normalization of this most of these patients will need to remain on drug, some will have, or most will have improvement in terms of their hormone prolactin level but persistent elevation may remain in these particular patients and again tumor volume was probably the most important but also that the initial prolactin level before the procedure was in the lower range rather than some of these patients with sky high levels. So if the prolactin level is quite high over 200 here then the tumor control rate as we see here in terms of normalization is very, very low compared to patients where the prolactin level is statistically significant if it's less than 200. Similarly for tumor volumes which allows us to give a higher dose, smaller tumor volumes are going to have a much more likelihood of normalization of prolactin level than the bigger tumors.

Again no patient developed optic neuropathy, no other new cranial nerve deficits and one patient developed a new hormone axis loss, some of these patients required additional resection, one went on to radiation therapy with a large invasive tumor and one patient had repeat radiosurgery. If we look at prolactinomas in terms of hypopituitarism risk, it's still in the range of about 1 out of 3 patients over the course of time, but overall we think for prolactinoma that it's an important adjuvant management for patients who have failed medical and surgical options, usually with laterally placed tumors in which we can use it.

I'll conclude with just a few comments about this disease which in fact extremely difficult as well because we are now dealing with patients who have failed surgical management and who are either intolerant or can't take suppression medication in which we are trying to achieve this type of, this



type of goal. 51 patients with clinically active Cushing's disease, 10 were lost to follow-up so we can't tell you about those, so we have 41 patients left in the series. 95% prior surgical resection and 5 who had had radiation therapy, most of these patients of course are used with suppression of cortisol production with Ketoconazole and about half the patients, about half the patients already had significant pituitary hormone loss with this prior, due to prior treatment. Trying to give much higher doses, these tumors tend to be smaller, symptoms are quite dramatic for tumors that are often so small and sometimes hard to image on the postoperative scan. So tumor control has been quite good in terms of prevention of further growth of the tumor either seeing shrinkage or no further growth with 4 patients showing progression. However in terms of the endocrine outcome, total remission in 44% of patients with 40% showing persistent elevation of factors measurable for Cushing's disease.

Again no complications related to this type of – however about 25% incidence of a new pituitary hormone axis in patients who have had the procedure, that's sort of in the ballpark of what some of the other series are in terms of this. This is probably the one with the largest reported delayed hypopituitarism risk which may be related to using very high dosages in a single treatment to this tumor equivalent to basically giving almost 130 grade of fractionated reduction therapy, so 4 times what we can give by usual radiation therapy techniques.

So for Cushing's disease we can attain tumor growth control in these refractory tumors in most, endocrine remission is more difficult to achieve but when it does it may eliminate the need for lifetime suppression therapy in patients and radiosurgery certainly seems to have a reduced risk of additional hormonal axis loss in comparison to more conventional radiation therapy types of

techniques, and perhaps over the course of time this may reduce lifetime management costs and of course all of us are trying to spend a lot of time trying to reduce the cost to our government so that it doesn't go bankrupt and we are no longer at 15% medical healthcare needs.

So that's basically a summary of the work related to these patients that we've done with our technology as an adjuvant to microsurgery and to endocrine management of these patients. The procedure itself appears to be low risk of comorbidity, has the best results in patients in terms of those who do not have functional tumors and has a moderately good success in the patients who have failed surgery with, with endocrine active tumors. Thanks very much.