

GAMMA KNIFE STEREOTACTIC RADIOSURGERY FOR NONFUNCTIONING
PITUITARY ADENOMAS
L. DADE LUMSFORD, MD

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Thanks, it's a pleasure to be here. I think one message from today's meeting would certainly be that the management of these problems is multiple different teams and those teams are critical to have the success with patients both from the surgical option the radiosurgical options and endocrine management and these are fascinating problems and the best results are going to occur when all these options are available for our patients.

So the first part I'm going to talk about is nonfunctional pituitary tumors, hormonally inactive tumors, that's the more common of the types of problems that we're asked to get involved in and we also have a team of people with whom we're working and several of our Fellows help to put together this data, Dr. Park, Dr. Mew who's actually here in the room. I'd like to thank them for their help in this as well.

So the goal of this is you want to get rid of the tumor or make it inactive, stop it from growing as we'll see in the hormone active tumor we want to stop hormone production and try to maintain the pituitary function. And together it's the combination of all of these things that is the best result. A lot of people get confused about what is this all about and we broadly lump surgery, medical management and radiation all into the same portfolio. But really there are different forms of how radiation is delivered and what's commonly thought of as radiation therapy which is done with multiple different treatments over the course of say 25 to 30 fractions is widely different, wildly different from what we're doing with radiosurgery.

And while this represented a standard of management for patients in years past when really not outcome data existed related to options such as radiosurgery, many patients ended up with similar types of improvement perhaps but the cost was much higher in terms of delayed hormonal function loss and I'll show you some of the data related to that.

The concept of fractionated radiation therapy is it's being done over the spreading of time and it's being done in order to reduce morbidity, not being done to improve response rate of the tumors that are treated. It's sort of based on the concept that if we're giving everything in the same general area the same dose, tumors that have a higher cell division rate than do late responding normal structures such as the blood vessels, brain and cranial nerves we'll get away with it but we won't need to worry as much about that for radiosurgery.

So what is radiosurgery? Radiosurgery is the single surgical procedure that uses a highly conformal delivery of multiple radiation beams that are cross-fired on a target. It is defined by intraoperative imaging with a goal of trying to biologically inactivate the target tissue in a single procedure so the wheels in the wheels out like we do other surgical procedures.

The device that we put in Pittsburgh in 1987, the first of 8 subsequent types of modifications was a device called the Gamma Knife, that was the fifth one in the world at that time, there's very little outcome data related to it. The original device had 201 x-ray beam with cobalt sources that cross-fired these gamma rays emitted from the cobalt sources on the target. A general concept of why this

works is that in a single treatment the radiobiological effectiveness the kill rate is about 4 times what we would see in the conventional fractionated radiation therapy. So if we can give a tumor in a single gamma knife procedure 12 Gy at the edge of this tumor, that's essentially equivalent to giving 48 Gy the standard fractionated dose we give with radiation therapy.

But the reality is since we're treating a tumor on the edge giving 12 Gy, if within the tumor we're getting four times that amount at some point, in essence a dose equivalent to almost four times what we can safely give by fractionated radiation therapy. And that's why it has a superior response.

So this paralleled the development of imaging tools and it was critical to have the right imaging tools and many of you aren't old enough to remember like me the first CT scanner that arrived at UPMC in 1975. This was a very rudimentary tool compared to what you've seen today in terms of MRI imaging. But the first therapeutic device which was linked with these kinds of things was the gamma knife which we put in in 1987 and of course now we see with high resolution 3 T imaging, we needed a knee device which was a parallel development in this field and that's what the current gamma knife looks like.

So I'm going to show you – we don't have a lot of movies to show you so I want to show you one, it shows you a little bit about what the gamma knife actually is. Within this thing that looks like the old mercury space shuttle, there are 192 cobalt sources which generate photons beams that are cross-fired on a target point inside the skull. And this has robotic movements which can actually allow us

to change the beam diameters between 4,8 and 16 millimeter beams which combine to destroy the target. These beams pass through the head, through the scalp, through the skull, there's no surgical incision, there's no opening because photon beam calculations can be used to determine what is the attenuation of each beam as it passes through the tissue before it summates on the target. We can actually mix beams together using a combination of very small beams in a single isocenter or what's called shots in our terminology to cover the 3D geometry of this type of tumor. And this effect is designed to be able to cause the tumor to inactivate.

So over the years the devices have changed, we have two devices here the 4C device and the current Perfexion device which as you see has a lot more room in it and allows us to treat tumors that are much more widely scattered in the head. This particular discipline is a classic example of disruptive innovation and in our field what we started out thinking was that this would be something used for tumors that were really unsuitable for surgery and so that's what it's initial role was. But then as the results began to accumulate over 25 years, it became well we can use it for residual tumors, vascular malformation and sometimes as a primary management and now its growth in – is really a primary management for many benign skull-based tumors.

In a 24 year experience we're over 11,000 cases at this particular center. As you can see the pituitary tumors are not the most common indication and that's because of the success that Paul has outlined related to surgical removal of these tumors. So in many ways we're like the clean up hitter for patients whose surgery can't be completely successful. Whenever you're the cleanup hitter that

means that your results are never going to be as good as the primary management option because you're ending up treating patients who have generally failed the initial surgical procedure.

So in our pituitary tumors, 83 percent of these patients had prior surgery, relatively few of them had already failed radiation therapy as well. And these tumor volumes tend to be relatively small, we're trying to give dosages that are in a single treatment at the edge covering the tumor wall.

Originally we thought that we could only treat small tumors that are far away from critical structures such as the optic nerve and chiasm. So a tumor like this that's grown back after the original transmodal type of operation and we can craft using the current technologies, very sharp treatment plans which confine the dose to the 3D geometry of this tumor seen in these various planes. But at the same time restrict the dose so that it sharply falls off, that the dose within critical structures such as the optic nerve and chiasm is extremely low.

There's another example of this in a patient where is regrowth of the tumor, we can outline the critical structure such as the optic nerve and then we can track the dose which covers the 3D geometry including the component that goes out into the cavernous sinus and treat this particular tumor.

Here's a residual pituitary tumor with right cavernous sinus and Paul has outlined beautifully the new advances that the endoscopic approach allows. But in those cases where there has been either

residual tumor or regrowth of this particular location, you can now use radiosurgery to treat this tumor in a very conformal way. So these two procedures fit together hand in hand.

Similarly a more difficult outline tumor, we're also keeping dose low in the pituitary stock because we want to make sure that the dose in that is restricted so we don't have a high risk of developing further endocrine dysfunction.

A typical example of a nonfunctional tumor might be a 29-year old patient with residual nonfunctioning tumor, he's already had two prior surgical procedures extensively lateral to the carotid here and 40 months later we see significant regression of the tumor.

So in our series of 125 nonfunctional patients up to 2009, these patients mostly were after surgery. Relatively few of them are having primary radiosurgery. Most of these were residual over current tumors and it's being used as an adjuvant or salvage method in these patients.

We look at the structure of where it is, the involvement as you see, many of these are patients who have had lateral cavernous sinus involvement or suprasellar extension and the structures which we're keeping a close eye on is related to how close it is to the visual structures, we want to track the visual function before and after the procedure as well as cranial neuro problems and of course we want to look at endocrine function. Only about a third of these patients have normal endocrine function prior to radiosurgery, many of these patients already have hypopituitarism of one degree or another.

We're looking at the dose and we're trying to follow these patients in this case over about 5 years or so in terms of treatment. We look at long term tumor control for the nonfunctional tumors and we see that over the course of time at one year about 99%, at five years 94% but there is some late failures as we get out to ten years of patients using this ____ type of analysis for tumor control.

And we're looking it related to tumor types, a new tumor versus residual tumor versus a recurrent tumor. Long term tumor control rates are in the close to 90% range. We didn't find that how close they were to the optic nerve was important to this, they're still overall in the 80 to 90% range. When they're a little bit closer to the optic nerve we may have to restrict the dose a little bit for safety and perhaps in this group of patients because of dose restriction their tumor control rate is about 10% less.

Then we looked at the multivariate analysis in terms of what are the factors that can allow us to predict better tumor control. And clearly larger tumors are more of a problem in both multivariate univariate analysis and is significant. And also whether this represents the first or second recurrence of their tumor was also highly significant which could be looked at from the Kap-Meier approach. So smaller tumors 95% tumor control rate, larger tumors down to 78% tumor control rate and that by the time you get out to 10 years when there's a larger tumor, down to about half the patients who have long term tumor control rate.

This is similar to patients with first recurrence versus two or more recurrences after two or more failed operations. Then we can see that the results are better when the patient is treated soon after the first definition of recurrence or residual tumor. So the point of this is don't wait. In our view since the tumor control rates are much better in this situation, it doesn't make any sense to us to say do subtotal removal or see that the tumor is growing and then just watch the patient to see what's going to happen.

If we look at the visual function in this – no patient has had a worsening visual function who had normal vision before, four patients with visual dysfunction because the tumors are very close to the optic chiasm – four patients had worsening vision but three of these were related to continued tumor progression and only one in a patient that had a stable tumor volume.

What about hormone function which of course is the most important to the patient in our endocrine teams. And in general for patients who had normal hormonal function before radiosurgery, 12 patients had worsening hormone function and for patients who either had partial deficits again about 25% of patients and these are the most common deficits that were noted over the course of time, ACTH thyroid stimulating hormone and growth hormone and very low incidence of developing any evidence of DI.

So what is the overall rate over time of developing some additional hormone loss over the course of time, it actually builds over the course of years, at 5 years it's about 29%, by the time you get up to

48% about half the patients at 10 years have developed some degree of a new at least single axis reduction so that they may need to be replaced either with cortisol primarily or a Synthroid.

There are factors that could affect the additional risk of hormone loss. Certainly if they had prior radiation therapy so this now represents a cumulative dose to the pituitary gland, that was a significant factor that increased the risk of subsequent hormone loss in this group. So again, in a Kap-Meier, prior radiation therapy versus no prior radiation therapy much higher rate of developing at least one new hormone axis lost.

If we look at this compared to fractionated radiation therapy, there are a number of papers that expand many, many years and this is only looking at really the most recent interval because this represents the interval of time when radiation therapy, fractionated radiation therapy had quantum leaps in terms of how it was being delivered, using intensity modulated radiation therapy techniques and computer imaging. Still the rate of hormone loss with hypopituitarism over the course of patients was in 50 to 70% of patients. As opposed to other reports from other centers using gamma knife radiosurgery where the rates range from only about 6% up to about 40% so overall about 50% less risk of developing a new pituitary hormone loss compared to fractionated radiation therapy.

So in summary for the nonfunctional tumors, if we look at this tumor control rate initially very high at 10 years goes down to about 75% of patients. And the poor response factors are the tumors that are already at larger volume and have had two or more prior operations and have residual tumors. In

terms of the risk of developing a new hormone deficit 25% is an average of about two years but significantly increase with prior radiation therapy. And it goes up over the course of time so maybe by the time ten years are out, almost half the patients may have at least one new axis loss.

The risk of other complications is extremely low. So no patients, only the one with the decline in visual function related to stable tumor treatment, again a very low risk even though most of these patients are patients being treated for tumors that are invasive of the cavernous sinus of developing other cranial nerve dysfunction related to locations in the cavernous sinus.

So for the latest in nonfunctional tumors, we think it's a safe and effective treatment, actually if we look at data on terms of Centers that are using this technology, over 25,000 pituitary tumor patients who have had the gamma knife worldwide. There are now hundreds of peer review publications, a book was just released by Sheehan and Lawson sellar, suprasellar tumors which has a very nice listing of all the publications related to various treatment strategies including surgery and radiosurgery.

The most common complication over the course of time at least by 10 years is the risk of at least one new pituitary hormone axis but the rate of pituitary hormone loss is significant lower with radiosurgery compared to radiation therapy. And just remember that – of our tendency is to try to lump everything into nice little pots, that this not the same type of procedure as what is being done with conventional fractionated radiation therapy.

So we think it's indicated in residual, progressive and recurrent tumors and we'll talk a little bit about the hormone reactive tumors next. It can be considered in certain newly diagnosed tumors, that is with patients who don't have optic neuropathy related to visual compression but who may have major other medical comorbidities for open surgery. For rejection fraction of 20%, 5% or something like that, you may not want to do even transmodal surgery. And we now know after years of experience that even tumors that are adjacent to the optic nerve can be treated effectively with the current strategies which allow us to spare dose into critical structures even very close to the tumor itself.