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Fluorescence-Guided Brain Surgery

DIRECT INTRAOPERATIVE VISUALIZATION OF A BRAIN TUMOR LEADS TO MORE COMPLETE RESECTION AND HOPEFULLY BETTER OUTCOME

Do outcomes in survival following brain tumor surgery correlate directly with the completeness of the resection?

You're listening to the Clinician's Roundtable on ReachMD XM 157, The Channel for Medical Professionals.

I am Dr. Bill Rutenberg, your host, and with me today is Dr. John Ruge. Dr. Ruge is the director of the Midwest Children's Brain Tumor Center at Lutheran General Hospital in Park Ridge, Illinois, and an assistant professor of surgery at Rush Medical College in Chicago.

Today, we are discussing optimizing the patient outcomes in neurosurgery by direct intraoperative observation of the brain tumor.

DR. BILL RUTENBERG:

Hi John! Thanks for joining us at the Clinician's Roundtable.

DR. JOHN RUGE:

Thank you very much for having me.

DR. BILL RUTENBERG:

So an answer to my question, do outcomes correlate directly with the amount of tumor removed?

DR. JOHN RUGE:

In general, yes. It's very clear in children that they do for most tumors. In adults because of the infiltrative nature of some of the aggressive tumors, it's more controversial.

DR. BILL RUTENBERG:

The current state of tumor visualization now, what is your technique doing to make it better?

DR. JOHN RUGE:

This technique is a technique utilized in Germany and other countries for several years now, but it's the technique that allows the tumor cells to fluoresce when given a dye.

DR. BILL RUTENBERG:

That's meaning, you can just see them?

DR. JOHN RUGE:

Yes, in the operating room after we have removed what we think to be the entire tumor, a special wavelength of the light is shown on the operative field and the tumors will glow like red charcoal.

DR. BILL RUTENBERG:

What is the material that's put into the tumor and how does it get there?

DR. JOHN RUGE:

It is called 5-ALA or 5-aminolevulinic acid and it's actually a normal or natural metabolite and hemoglobin synthesis. It's given orally 3 hours before surgery.

DR. BILL RUTENBERG:

And then it's taken up specifically by tumor cells or are there any other tissues in the brain that are taking it up?

DR. JOHN RUGE:

Well, there is a low level of activity, but it's taken up, it's been found in malignant tumors of the brain, exponentially higher concentration.

DR. BILL RUTENBERG:

This procedure, is it being done elsewhere in the United States or how did you get involved with the project here in America?

DR. JOHN RUGE:

Approximately 5 years ago, I went over to Munich, Germany, to learn the technique with Dr. Stummer, who is really the lead man in this field and the developer of this technique, and I was interested because I saw his early publication and I thought yeah! this showed a lot of use in adults, but I was fascinated with the possibility of using it in children.

DR. BILL RUTENBERG:

Are you studying this under an NIH grant or how is the funding coming for the project?

DR. JOHN RUGE:

The funding is from our Midwest Children's Brain Tumor Center in the IRB-approved phase I, phase II protocol.

DR. BILL RUTENBERG:

Was there any difficulty in getting this through the IRB, Institutional Review Board at Lutheran General Hospital?

DR. JOHN RUGE:

No, not really and this is sort of the normal precautions and it went through fine.

DR. BILL RUTENBERG:

Now what makes this a significant step forward, we have PET scans, SPECT scans, intraoperative MRIs. What does this do differently for you as a neurosurgeon?

DR. JOHN RUGE:

For a neurosurgeon, we can image the tumor or image the area of the tumor very well preoperatively, but once you are actually operating on the tumor, the center of the tumor is very obvious and you know straightforward to remove, but once you get to the margins, it becomes more difficult to determine what is tumor and what is normal brain, and so we need any how possible and the ability to sort of color code the surgery where it distinguishes tumor from normal brain is a huge help to achieve a more total resection.

DR. BILL RUTENBERG:

What type of brain tumors have this technique been applied to and specifically what's your experience so far?

DR. JOHN RUGE:

Well, my personal experience is limited, the German experience and now Japanese experience is quite extensive, but this dye is used for malignant tumors of the brain in adults and children and the Germans have done as a collaborative study over 200. We did our first case, I believe, in the United States here in April and did the first child ever to use this technique in August.

DR. BILL RUTENBERG:

And what type of tumor was that for?

DR. JOHN RUGE:

Well in the adult it was the same type of tumor that the Germans were using, it was a glioblastoma and the child was a, what's called, PXA, which is a more benign type of tumor and surprisingly lit up and it was extremely helpful in allowing us to remove the total tumor.

DR. BILL RUTENBERG:

And the child is doing?

DR. JOHN RUGE:

The child is doing perfect.

DR. BILL RUTENBERG:

With gliomas, I guess, because they have sort of this insidious way of inserting themselves throughout the brain or through normal tissue, how small an area can they visualize? I mean we are talking, you know, 1000 cells, a centimeter does it have to be before you see it, how big in area or small in area can you actually see?

DR. JOHN RUGE:

Yeah, it's a good question. The tumors tend to be, by the time they present or become symptomatic, are quite easily seen most of the time on MRI studies. In surgery, as I mentioned, the center of the tumor is usually pretty obvious, and then at the end of the operation when you think you've got it all under the microscope, we experience I think that it will be what looks like mostly clean, but then may be a little nodule that goes probably measuring in the matter of 3 or 4 mm sometimes and then that can be removed.

DR. BILL RUTENBERG:

Afterwards is this fluorescent dye, does it enhance say on a postoperative MRI?

DR. JOHN RUGE:

No, it doesn't.

DR. BILL RUTENBERG:

So you have to see it. Now, does it have to be on the surface or you know how deep within the brain structure will this dye appear.

DR. JOHN RUGE:

Yeah, that's a good question. It relies on the penetration of the blue light that is shined on it, so it has to be indirect exposure to the blue light so if the blue light is transmitted through several cell layers, the fluorescence will occur, but if there is a layer of blood or debris over the tumor, the tumor will not fluoresce.

DR. BILL RUTENBERG:

I would like to welcome those who are just joining us at the Clinician's Roundtable on ReachMD XM 157, The Channel for Medical Professionals. I am Dr. Bill Rutenberg and with me today is Dr. John Ruge, director of the Midwest Children's Brain Tumor Center in Park Ridge, Illinois. We are discussing how direct intraoperative visualization of a brain tumor leads to more complete resection and hopefully better outcome. So it's pretty much a surface marker than the fair take-away message.

DR. JOHN RUGE:

The entire tumor takes up this dye, but we only interact with it at the surface.

DR. BILL RUTENBERG:

Now, as you get down to lower levels, do you sort of shine the light again and you go step by step, you sort of kind of like an archaeologist sort of taking away a layer of dirt at that time.

DR. JOHN RUGE:

That's exactly right, that's good analogy. The microscope is adapted with a little toggle switch that will switch between the excitation light and a normal white light and so we toggle back and forth as we operate and like an archaeologist goes deeper and deeper in the tumor.

DR. BILL RUTENBERG:

In Germany and perhaps Japan where there has been more experience, I think you've said 10 years of experience, has this become a standard part of their surgical routine for brain tumor surgery?

DR. JOHN RUGE:

In Germany, yes, and you know what's remarkable, I was skeptical about this technique until I used them. I really am excited about because I think it will in certain tumor types allow the neurosurgeons to do a better job, so I hope that other neurosurgeons, I know there is a great deal of interest now, and I am sure it will become a part of the technique.

DR. BILL RUTENBERG:

Now, for neurosurgeons themselves, who are interested in learning more about it, is there any place they can go to in this country, are there any conferences upcoming?

DR. JOHN RUGE:

Well, we do have a conference that we are inviting; the Germans will be there, Dr. Stummer, and the Japanese, October 30, in Chicago.

DR. BILL RUTENBERG:

And for more information, some physicians are interested in attending, how would they get more information?

DR. JOHN RUGE:

They can contact our center or call 847-723-5105.

DR. BILL RUTENBERG:

Is there a website as well if they want more information?

DR. JOHN RUGE:

Yes, they just search on the Midwest Children's Brain Tumor Center in Park Ridge, google <_____> and they'll get to it.

DR. BILL RUTENBERG:

They'll get to this conference. Is this a one-day conference?

DR. JOHN RUGE:

Yes, it's just a symposium. It's focused totally on 5-ALA and brain tumor resection. We're going to go over how to institute a protocol like this in your hospital in United States and how we went through the FDA and the process and also look at what is next in horizon with really the true leaders in the field from Japan and Germany.

DR. BILL RUTENBERG:

Can you give us any insights? We are always looking for what's next on the horizon.

DR. JOHN RUGE:

Well, you know what, I think what's coming up is that this is going to be used in children and in tumors that are not totally malignant, but over a great diversity of tumor leading to the tremendous advance in our ability to take care of these children.

DR. BILL RUTENBERG:

I have a particular interest in meningiomas as you may know and is that a tumor that you would use this in?

DR. JOHN RUGE:

Actually, no, that tumor is usually pretty well demarcated on its own and typically benign and doesn't impose the same problems usually.

DR. BILL RUTENBERG:

Could you use it in another words like sometimes these tumors are close to the optic nerve or the carotid artery and you know you want to get as much as possible? Could you use in this situation like that?

DR. JOHN RUGE:

Yes, that is the case, it's useful that I should be very selective on which tumor types to use and we're learning more about the applicability of this, but yes we need to distinguish what's tumor and what's critical structure. It's another technique and I think it's going to serve an important role.

DR. BILL RUTENBERG:

As of now, what tumor specifically in children would you be using this technique for?

DR. JOHN RUGE:

The malignant tumors, and it has not been shown yet, you know, that's why we are doing the study, exactly, which tumors will take this dye up. We know in adults it's the most common malignant tumor, unfortunately most common tumor in adulthood, which is a glioblastoma, but in children it's an area wide open for research.

DR. BILL RUTENBERG:

And so, say on your list, you went through an IRB, so I assume you probably had to give them some specific diagnoses. Could you tell us which ones are currently approved at Lutheran General Hospital?

DR. JOHN RUGE:

Yeah, basically all the malignant tumors, so astrocytomas, glioblastomas, anaplastic astrocytomas, or malignant tumors such as ependymomas and medulloblastomas.

DR. BILL RUTENBERG:

And then you said for the benign tumors, so currently that's the upcoming area of interest, I guess, that's the hot area?

DR. JOHN RUGE:

That's right. In some of these tumors you can't tell, sort of biopsy on, if there are malignant or nonmalignant and the one 8-year-old girl that we operated on with this with a benign tumor, we initially thought it was a malignant tumor, so it was surprising that this tumor dye took up, and it really did. When it was done during the surgery, I thought I was done and fluoresced the field and there was a little nodule and I took it and I sent it for biopsy to see if it was tumor or non-tumor right away and indeed it was tumor and I would have left that otherwise, and the girl has also now avoided the need for radiation after surgery because of this.

DR. BILL RUTENBERG:

Ah, so that's another definite positive upside risk. Are there any downside risks to this procedure?

DR. JOHN RUGE:

Yes, unfortunately, the 5-ALA is a normal metabolite and so the body is used to it. We do give it in higher concentration and it's not indicated in the people, who have porphyruria or hemoglobin synthesis problems, and the downside is that if you are exposed to sunlight or ambient light for a period of 24 hours, it can cause an itching reaction or rash on your skin, and so we keep these people in a darkened environment for 48 hours after surgery while it's eliminated from the body.

DR. BILL RUTENBERG:

Is there anything that keeps you up at night worrying, you know, you are getting ready to go into surgery, is there anything about the technique or the procedure?

DR. JOHN RUGE:

The only thing is that the absorption of it. We had one child that we didn't fluoresce. It was given several hours before surgery and the anesthesiologist from before placing the tube to intubation aspirated 200 mL of fluid out of the abdomen and I think also aspirated our dye out, so the absorption of this is something I am somewhat worried about sometimes.

DR. BILL RUTENBERG:

In the United States can we consider this an up and coming standard for brain tumor? Do we have enough evidence from around the world that other neurosurgeons could begin to apply this technique here?

DR. JOHN RUGE:

Certainly for adult glioblastomas, in those particular situations where the goal is a complete resection. There are certain tumors with <_____> and location that that is not the goal. The goal is to decompress and subtotally resect, but that I feel comfortable though. We have more to do in establishing it as useful in another tumor types.

DR. BILL RUTENBERG:

I would like to thank Dr. John Ruge who has been my guest at the Clinician's Roundtable on ReachMD XM 157, The Channel for Medical Professionals.

I am Dr. Bill Rutenberg and we've been discussing how intraoperative visualization of brain tumors lead to more complete resection and hopefully much better outcomes. Thanks for listening. I wish you good day and good health.

This is Dr. Anthony Jahn from New York and you are listening to the first national radio channel created specifically for medical professionals, ReachMD XM 157.