



## Outstanding Questions from Webinar: Long-Term Survival Outcomes for LGG Patients, May 5<sup>th</sup>, 2014

Answers provided as a courtesy by Dana Farber Cancer Institute experts:

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1. Please give implications of IDH1 mutation in children with LGG.  
IDH-1 mutations are extremely rare in the pediatric population. As such, very little is known about the prognostic significance of this mutation in the pediatric population. In the adult population, IDH-1 is associated with treatment response but over the long-term, increasing malignancy. However, adult and pediatric gliomas have a very different natural history and it is unclear what, if any, prognostic significance IDH-1 mutations have in pediatric patients.
2. Is there any research which explains if puberty (i.e., role of hormones) has an impact in the development and changes of LGG  
Many patients and their families are concerned that puberty may accelerate tumor growth, or initiate a relapse. There is no evidence to suggest that this is the case. In some cases we even administer growth hormone to patients with low grade gliomas and this has not been correlated with tumor progression.
3. I keep hearing when it returns or when it grows. Is it a given that we expect relapse?  
Following treatment with chemotherapy, approximately 60% of patients will have tumor growth again in the future. Though many children will only require one treatment, most children will require therapy more than once in their lifetime. Even in patients who do have progression, the overall prognosis for children with low grade gliomas is excellent. The average time to tumor progression in patients who do progress is 3 years. That means that some patients progress in one year, others in 5 years and others never progress. Children who are very young when they are initially diagnosed are more likely to require multiple treatments.
4. I have an almost 15 year old diagnosed two years ago with a low grade glioma in the optic chiasm and along the optic nerve as well as the pit/hypo glands. He is still being monitored with MRI's and there has been a slight change in size over the last 2 years. He was probably 4'8 when diagnosed but is now 5'3 and



growing so we're hopeful he'll get to a normal height. Given his age and height, our doctors in NY now think he could be a good candidate for radiation when the time comes. We had been advised that radiation was not an option given the optic nerve and gland involvement. We also understand that targeted therapy could be an option down the road. Any thoughts on the promise of one v. the other?

Radiation is effective therapy for low grade gliomas. However, it is associated with several severe late effects (side effects that present after treatment). These include cognitive impairment, stroke, hormone deficiency and secondary malignancy. Given your son's tumor's proximity to the pituitary gland, he is also at high risk of developing multiple hormone abnormalities with radiation therapy. Since there are multiple chemotherapy options, and as you point out these are improving all the time, it is our practice to reserve radiation therapy for patients who have not responded to multiple chemotherapy regimens.

5. What is the role of proton therapy in the treatment of LLG? If radiation therapy is being considered, there may be advantages to proton beam RT, depending on the location of the tumor. However, there is not a clear advantage of radiation therapy to chemotherapy in the long run. Therefore, chemotherapy is still the preferred treatment upfront and in recurrence/progression of tumor.

6. What about kids that had a PA at a younger age (say 14 ) and then the tumor returns as an adult (25)? Is survivorship as good as the kids or does it drop as they are an adult?

Survival increases in patients over the age of 23 from about 83% to 91%. In the patients we see with LGG, if they recur as adults, they typically are still PA. If a patient had radiation therapy, then you need to consider if the tumor returns, is it a secondary radiation induced malignancy.

7. Does IMRT or Tomotherapy Radiation improve the outcome long term for teens that had been radiated

We generally do not re-irradiate patients with LGG, regardless of age and these specialized radiation techniques still have considerable long term risks.

8. How often do these tumors become "dormant" in adulthood?

We feel that they do become dormant. When we reviewed over 4000 children with LGG, the survival rate in patients over 23 was higher than in those over 23. We were unable to determine if cause of death in these patients was due to prior treatment (radiation) or the primary tumor but the fact the survival rate improves the older the patient speaks to this fact.



9. Can you elaborate on the statement 'that after 20 yo biology takes over' (one of the last slides)? What changes at that age?

This is an area of active research. There are genes and genetic modifications that take place in children that are known to assist in development. At this moment, we do not know what genes may “turn off” after childhood that may make a low grade glioma stop growing in adulthood, but hopefully our ongoing research will answer this question.

10. Will there be alternatives to craniotomy to resect tumors in the future? (Ours is right temporal lobe near hippocampus, remaining lesion after resection.)

There may be, but surgery is still the standard for diagnosis. As we move into molecular characterization for tumors that can assist us in defining treatment, tissue will be needed for this via biopsy. We do know that children with biopsies do very well in terms of outcome and therefore, surgery does not need to be aggressive. With intra-operative imaging and computer-guided biopsies, injuries during surgery are less likely now.

11. Does the length of time that growth occurs impact future growth and recurrence? ie - if there is growth within 6 months of dx

No, there are some tumors that do not respond to initial therapy but will respond to 2nd or even 3rd treatments.

12. How many years after treatment do we see the toxicity effects of radiation? It is variable. If you had radiation exposure to your pituitary gland or hypothalamus, you may develop endocrine (hormone) issues, most commonly hypothyroidism and growth hormone deficiency. These usually develop 1-2 years after radiation therapy and you can ask your oncologist or radiation oncologist if you are at risk for this.

Cognitive deficits are also an issue that needs to be evaluated soon after treatment is completed and continue to be an issue all through development and into adulthood. We recommend that our patients see a neuro-psychologist for testing to identify any areas of learning impairment. This can then be shared with the school to develop individualized education plans (IEP) to ensure that each child's educational needs are met. Common issues include memory, speed of processing and organizational skills.

There is an increased risk of secondary malignancies, which are tumors caused by the radiation. These usually occur at greater than 5 years post radiation.

There are two types of tumors that are typically seen. The most common is a slow growing tumor called a meningioma. This is a tumor of the covering of the brain. If this is found and there are no symptoms, we typically do not operate or



treat these tumors and will monitor them with serial MRI scans. If they continue to grow, surgical resection is the best option. The second type of tumor is a high grade glioma. This is not due to a transformation of the original tumor but rather it is due to damage to normal glial cell during radiation. Treatment for this type of tumor usually involves maximal surgical resection followed by radiation and chemotherapy. With current treatment strategies, the outcomes for this tumor are poor.

The last is an increased risk of stroke. This also occurs after 5-10 years from radiation. There is no data to support use of aspirin to prevent strokes in patients after they receive radiation. The most important preventative strategy is to limit other risk factors such as obesity, high cholesterol and high blood pressure. We encourage our brain tumor survivors to engage in healthy lifestyle choices including diet, exercise and to refrain from smoking.

13. Dr. Kieran mentioned that some kids pilomyxoid astrocytomas present more significant complications in the early years - why is that and what form does/can that take?

Pilomyxoid astrocytomas often arise deep in the central part of the brain and cannot be removed surgically. They are the most common low-grade glioma that metastasize (spread) to other parts of the brain and spine (meaning patients often have multiple tumors) and they often start very early in life. They often cause severe malnutrition early in life and it is the constellation of these issues that result in the more significant complications.

14. Are there markers that would indicate the tumor would come back?

Unfortunately, there are no blood, urine or spinal fluid tests that predict when a tumor will come back (although we are working on this). As such, we rely on regular exams and periodic MRI scans to tell us when one has already started to regrow.

15. Is there any novel medicine, which not only can treat optic glioma but also can improve the vision of optic glioma kids?

The novel therapies for optic glioma, like other low grade gliomas, is based on the molecular profile of the tumor. All therapies, including chemotherapy, biologic therapy and radiation therapy can occasionally improve vision although how this happens is not always clear. Some patients will have significant shrinkage of their optic pathway tumor but no improvement in vision. Other patients can have no shrinkage in their tumor and yet have some improvement in vision.



16. Is there any information about the rate of return of low grade tumors in females when they become pregnant as adults? In other words, does pregnancy cause hormonal or biological changes that cause low grade tumors to grow or change in their malignancy?

There is no evidence that puberty or pregnancy increases the recurrence of pediatric low-grade gliomas.

17. What kind of treatments exist to reduce toxicity, for patients who have had radiotherapy?

Unfortunately, there are none. We work very hard to mitigate the effects of radiation therapy. For example, if radiation therapy knocks out hormone production, then we provide hormone replacement. We can help with educational support for the cognitive effects of radiation but cannot do something to undo them after the radiation has been given.

18. My daughter is on Avastin alone after not tolerating CPT 11. Avastin alone seems to keep her tumor at bay and she's currently on break from treatment for last 6 months. Have they found other drugs to use with Avastin that are showing promise or are you seeing Avastin alone is often sufficient. She's already had 2 yrs of Avastin with a 9 month break and now a 6 month break in between.

The choice of avastin and CPT11 was originally based on the treatment of malignant adult tumors. Over time, the need for CPT11 has been questioned as the data for avastin alone appears to be about as good as the combination but with much less toxicity (since most of it comes from the CPT11). While avastin has been helpful in some patients with pediatric low grade gliomas, progression after treatment is common. People are testing combinations although less so than before as the expense of the drug and need for constant intravenous administration needed for this drug has removed some of the enthusiasm for its use.

19. With respects to complete surgical resection many of the neurocognitive issues are similar to that of chemo or radiation but the children don't seem to get the same resources or support. Can you address that or make suggestions?

Neurocognitive issues after surgery are uncommon except for direct damage to the part of the brain where the surgeon operated. As mentioned before, this is why the expertise of the surgeon and the understanding that it is not necessarily for the surgeon to be overly aggressive is critical. Similarly, chemotherapy is a hassle to give, having to come to clinic every week, the acute side effects, etc., but long term cognitive issues for routine chemotherapy like vincristine/carboplatin are uncommon. Major centers should have a dedicated survivor program that help address these issues.



20. How often do you need a scan after chemo if you have finished an 18 month course?

There is no single answer and each center chooses its own standard. A common routine is an MRI scan every three months for the first year after completion of chemotherapy, every 6 months for a year and then yearly after that. If any new symptoms arise, an interim scan can always be obtained.

21. In assessing the tenure of the surgeon, is there a particular hurdle rate (# years) where you see a doctor's level of success have less variation? how many years of experience with these tumors should I look for in a surgeon as a minimum?

There is no single answer here. A dedicated pediatric neurosurgeon that focuses on children with brain tumors is what you are looking for. Usually, a pediatric neurosurgeon with at least two or three years of focused brain tumor experience is enough but as expected, depends a little on the innate talent of the individual.

22. Is the 20 year mark also true for Neurofibromatosis?

Yes, in fact, overall, patients with NF1 do better because their LGG are more likely to stop spontaneously than in patients without NF1. Important differences in patients with NF1 is that it is more common for these patients to have more than one low-grade glioma at a time and thus more lesions that we have to worry about. In addition, patients with NF1 are more at risk for other tumors in the body including peripheral nerve sheath tumors and a malignant brain tumor called glioblastoma multiforme. The reason for this is as a result of the NF1 mutation. Because of this increased risk, patients with NF1 should not receive radiation for any low-grade tumor, nor should they receive certain chemotherapy drugs (called alkylators) that could increase their risk of leukemia later in life.

23. Is the outcome the same if there is also leptomeningeal dissemination?

Having dissemination (metastases) in cancer is usually a particularly bad sign. In patients with low-grade gliomas however, the presence of leptomeningeal disease does not mean that the tumor has become more aggressive. Rather the spread of the tumor means that you have multiple low-grade lesions, all of which are in a constant state of stopping and starting growth. The major difference between having one lesion versus multiple is that in the periods of time where the one lesion has stopped, the patient is well, needs no therapy, and can focus on being a kid. When you have multiple lesions present (either as distinct masses, or as leptomeningeal spread), this means that at any one time, even if most of the lesions are in their quiescent phase, there may be a few in the active phase. As such, these patients often need almost continuous therapy, which can take a toll as a result of the cumulative toxicity.



24. Our surgeon has mentioned that at some point my daughter may need cyberknife treatment, does this type of radiation have the same toxicity as some of the others mentioned?

Cyberknife radiation therapy, also known as X-Knife, Gamma-Knife or Stereotactic Radiation Therapy (SRS) are all methods of giving highly focused radiation beams that concentrate into one area, much like focusing the sun with a magnifying glass. This type of radiation, rather than being given over 6 weeks (which is how standard radiation therapy is given), is done in one day and is meant to kill (burn, cook, liquefy or whatever term that you would want to use) the tumor in the center of the beam (just like you do burning a hole in a leaf under the sun and the magnifying glass). That is why all of the terms used for this therapy have the words 'knife' or 'surgery' in them. If this is like surgery, then what is the difference? The major change is that you can kill a tumor without having to open the skull (the radiation beams coming in at many angles focus only on the tumor). There are of course a number of issues with this approach. If you miss even a tiny piece of the tumor in the beam, it will come back. If you hit even a tiny piece of normal brain, it is lost forever. There are also significant size issues with this technique (it is only used for very small lesions). In general, if a lesion needs to be removed, it is usually better to have it done by a surgeon so that they can see exactly where they are and what they are doing at all times. There are only a very few examples where this type of treatment is preferred. With respect to the toxicity of these approaches, because the radiation fields are much tighter (given that they are going to destroy whatever is in the center of the beam), there are fewer risks (easier to avoid certain structures and the volume is smaller) so the cognitive risks are much less.

25. What do you consider long term survival for a child with an inoperable tectal glioma?

Patients with tectal gliomas have the best outcome of all children with low-grade gliomas. For reasons that are poorly understood, as these tumors grow, they block off the flow of the spinal fluid which causes a dramatic rise in pressure in the brain. This causes the acute symptoms that lead to the diagnosis. When the surgeon does a procedure to relieve the pressure (without even touching the tumor), in most patients, this causes the tumor to stop growing. Why this happens we do not yet understand but for most patients with a classic tectal glioma, the 3<sup>rd</sup> ventriculostomy diversion of the fluid pressure is the only treatment they will ever need.



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26. What is the typical tumor type we see secondary to a JPA from radiation treatment?

Radiation induced tumors are not related to the tumor that your child has, but rather the damage that the radiation therapy causes to other normal cells in the brain that become tumors. As such, all patients getting radiation therapy are at risk for the same radiation induced tumors independent of their initial diagnosis. The two most common tumor types caused by radiation to the brain are meningiomas, which are low grade and often treatable with surgery alone. The second type of radiation-induced tumor is called glioblastoma multiforme, a highly malignant and incurable tumor. This is the one we worry about. There are still debates about what the risk of these tumors are but we currently quote 5-10% of all patients getting radiation will get one. It is not clear that the risk of getting these tumors ever goes away after a child/adult has received radiation therapy.