Questions from Dr. Mark Kieran’s webinar – February 26, 2013

- What is the makeup of cysts?
  - Cysts are fluid filled cavities. The walls can be made up from a lining of tumor cells that secrete the fluid into the cyst. The actual content of the fluid can differ between tumors (the fluid in a craniopharyngioma cyst is different than the cysts typically observed in low-grade gliomas).

- Should the cyst flow be drained into the brain fluid or removed from the brain?
  - It depends a little on the type of cyst. It is not always possible to remove all of the cells lining a cyst. The surgeons will try to take them out but often can only remove part of the wall. While this will often prevent the cyst wall from coming back and thus the cyst from building up again (and so the operation was a success), the cells remaining behind can continue to produce fluid which gets reabsorbed naturally (and is usually well tolerated).

- Is proton radiation being done in Canada?
  - I do not believe that there are any proton radiation facilities in Canada. There are about 7 in the US (and more opening) and a number in Germany, Switzerland and France.

- You mentioned for medulloblastoma there's 4 different subtypes, WNT, SHH, and what are the other 2? Best prognosis?
  - The other two types are called Group C and Group D (aka Group 3 and Group 4). While I know these names are not very imaginative, this is in part reflected by the lack of a single pathway driving them. The sonic hedgehog pathway defines that pathway and the wnt pathway defines the wnt pathway. Also recall that some people consider there to be 6 subgroups, others 5 and still other 4. It depends on whether you are a lumper or a splitter.

- [What is the] best gold [standard] treatment right now for medulloblastoma? Prognosis for relapsed medulloblastoma?
  - The treatment for medulloblastoma depends on the stage of the disease and age of the patient. High risk medulloblastoma is defined as those patients with a large unresectable tumor, those with metastatic disease or those with the anaplastic/large cell subtype. For these patients, the standard treatment is maximal safe surgical resection, high dose craniospinal radiation therapy, a radiation boost to bulk areas of disease and chemotherapy. With this approach, the cure rate is about 65-70%. For standard risk patients (those with most of the tumor removed, no evidence of metastases and no evidence of large cell/anaplastic sub-type), the treatment is maximal
safe surgical resection, lower dose craniospinal radiation therapy, a radiation boost to the original site of the tumor and chemotherapy. With this approach, the cure rate is about 85%. There is one additional group of patients, called infant medulloblastoma. This group is defined as patients less than 3-6 years old (each group uses a different age cutoff) and the primary goal is to avoid radiation therapy (since the damage of radiation therapy is worst in younger patients). In doing so, we rely on maximal safe surgical resection followed by multi-agent chemotherapy. Some centers add in high-dose chemotherapy and stem cell rescue, some add in intrathecal chemotherapy. There is no international consensus on the treatment for these patients so in general, each site chooses one method and sticks with it. The prognosis is typically about 50% but it really depends on the child. You will also notice that none of these categories asked what the molecular subtype was as they do not incorporate this into the treatment decision. We do know that infants with the nodular desmoplastic subtype have a 90% cure rate without any radiation therapy and we are just starting a clinical trial to remove all radiation therapy for patients with the wnt subtype so these types of molecularly based trial are just starting. For relapsed disease, the prognosis is poor. While some centers use high-dose chemotherapy and stem cell rescue (a bone marrow transplant), the long-term cure rate is small, especially if the patient has recurred after having received radiation therapy.

- How often should MRI’s be done following tx?
  - The standard is every three months for 1 year, every 6 months for 1 year and then yearly after that. Some insurance companies want the scans to be a little less frequent and each center can modify these rules as they see fit.

- Can you share any updates on treatment for Pediatric low-grade astrocytoma?
  - This is a big topic and perhaps we need a webinar on medulloblastoma and another one on low-grade gliomas. With the discovery of many of the common mutations that give rise to low-grade glioma tumors, the presence or absence of certain genetic diseases (neurofibromatosis type I, tuberous sclerosis), their excellent long-term prognosis, and the availability of targeted therapies for them, each case needs to be evaluated for these variables to identify the 'optima' treatment approach.

- Re: anaplastic astrocytoma: Where can I see the list of places involved in this research?
  - There is research in anaplastic astrocytomas going on at centers around the world. Because these are less common than pediatric glioblastoma multiforme (GBM), they are often studied together. Because adult GBM and anaplastic astrocytoma are much more common (100x) than pediatric tumors of the same type, much of the data is based on adults. As we discussed in the webinar, this can be a problem as we have come to recognize the differences between the tumors by age (adult vs pediatrics). The initial pioneering work on pediatric high grade gliomas (this term combines anaplastic
astrocytomas and GBM) was done in the laboratory of Dr Nada Jabado at McGill University in Montreal, Canada.

- Are MRI's sufficient for long term follow up post full brain/spine rt + hdct?
  - In general yes. Unless there is a specific issue (seizures for example are sometime better identified by nuclear imaging), brain and spine MRI can assess for the recurrence of a tumor, development of a new radiation induced tumor, bleeding, vasculopathy (radiation induced damage to the blood vessels of the brain) and hydrocephalus. If a problem is identified, then additional imaging could be needed. For example, if there is radiation damage to the blood vessels, an MRA (magnetic resonance angiography) is sometimes helpful.

- Are there any examples in pediatric or adult brain tumors where the therapies mentioned have led to long-term remission?
  - For the most malignant diseases such as DIPG and GBM, there is insufficient long-term data to prove benefit. The success cannot be measured by going from rare survival to everyone surviving. Rather, as the treatment data comes in, we will see some patients that did no better than before, some who did better longer but eventually succumbed to disease, and hopefully a few more long-term survivors. As we continue to add on new agents to these (based on discovering new mutations), we expect to see a progressive shift towards more and more patients doing better, surviving longer and being cured. We also know that the analysis of tumor type (like the nodular desmoplastic medulloblastoma of infancy mentioned above) can and has already changed the therapy for these patient. For a disease like Tuberous Sclerosis low-grade gliomas, I showed an example of patients treated with the molecular inhibitor RAD001, which is now approved and commercially available exactly for this disease. After 60 years of traditional based radiation and chemotherapy, molecular therapy is only about 5 years old and so we have a way to go. I should point out that some diseases (like leukemia) are ahead of us in identifying the molecular subtype of the tumor and treating accordingly. While I believe that it is much easier to get lots of blood samples from a leukemia patient while we can biopsy the brain only once or twice, my leukemia colleagues tell me they are ahead of us because they are smarter.

- If you have a tumour that appears to be responding to treatment, but have not have DNA testing, would you recommend pushing to have biopsy and testing done?
  - Every circumstance is different but in general the answer to this question is no for two reasons. If a patient is responding to their current therapy, subjecting them to a risk like biopsy when you already have an effective therapy wouldn't make sense (although it would if the treatment wasn't working). The second reason is that we can now do almost all of the molecular profiling on the fixed tissue sitting in the pathology department (it doesn't need to be fresh anymore).
• Has there been a study compiled of children with DIPG that shows the congruencies between different pathways that respond to certain drugs that may be used for DIPG?
  o No there has not been, in part because our trial is the first in the word to base therapy sole on the molecular subtype of the tumor. Before, even when we used a molecularly targeted drug without a biopsy, every patient got the drug but we had no idea who had the target (if any). When the drug didn't work, we threw it away, not knowing if the 10 patients we tested it on happen to be 10 patients lacking that particular target.

• Are there any new advances with pilomyxoid astrocytoma tumors
  o The major advance is happening in terms of understand what mutations drive these tumors compared to all of the other low-grade gliomas. If it turns out to be the same (the sequencing projects are already underway), then we will be able to use the same set of drugs. If the mutations are different, then we will know what drugs we need to use, as well as which ones there is no point in using.