

The fine line between cancer and a cure

More than any other type of cancer, brain tumors are like Rubik's Cubes, those six-sided, multi-colored puzzles that require you to turn the pieces until each side is a solid color. The challenge with the Rubik's Cube is to complete more than one color at a time because, while each twist brings you closer to finishing one side, it invariably takes you further from completing the others.

Doctors who treat children with brain...



Photos: Mark Ostow



tumors face the same difficulty: the desire to do whatever it takes to cure a child's disease must be weighed against the all-too-real physical consequences of attaining that cure.

But there is hope. Today at Children's Hospital Boston, diagnostic tools allow tumors to be detected sooner and more accurately; new technologies help surgeons remove as much tumor as possible without damaging healthy tissue; radiation and chemotherapy are more precise; and the human genome has been decoded, raising the possibility that cancer can be detected and treated at its most basic level. But the question remains: Will any of this make a difference?

Inelegant solutions

While progress has been relatively rapid for other childhood cancers such as acute lymphoblastic leukemia, which now has survival rates of more than 80 percent, inroads have come more slowly for brain tumors. Even though they continue to be relatively rare—with fewer than 2,000 new cases diagnosed nationwide in children each year—brain tumors are now the leading cause of death from childhood cancer.

And these numbers don't take into account the side effects of treating the disease. Adults with brain tumors who are treated with the three traditional cancer therapies of surgery, chemotherapy and radiation can expect an array of problems ranging from hair loss and nausea to vision problems and seizures. But the same treatments in children—whose brains are still developing—can also have a significant effect on cognitive and physical development.

The facts about current treatments speak for themselves: A recent National Cancer Institute survey of more than 1,800 children with brain tumors—all of whom survived at least five years—found that nearly a third suffered seizures and blackouts; 37 percent had headaches and migraines; a sizable minority suffered hearing loss or blindness; 70 percent diagnosed before age 3 required special education or learning-disabled classroom settings; and, largely because more children are surviving their original tumors, secondary tumors caused by radiation and chemotherapy are on the rise.

It is because of these after-effects that brain tumor specialists find themselves tiptoeing through a minefield, trying to balance the benefits of each treatment against its side effects. The ability to attain clear and concise pictures of the tumor and the healthy brain around it is hampered by the fact that children often can't sit still for the hour or more it takes to complete a magnetic resonance imaging (MRI) scan. The desire to surgically



remove the entire tumor is tempered by caution, lest areas that control speech or other essential functions be taken out as well. And the hope of destroying cancer cells with radiation and chemotherapy is balanced against the fear of damaging healthy cells as well.

The tales of two tumors

The experiences of two Children's patients illustrate this balancing act and prove that with brain tumors, solving one side of the Rubik's Cube is not enough.

Eight years ago, Chris Johnson was the 12-year-old all-star catcher for his town baseball team when he started seeing two pitches coming at him instead of one. At first he was told the cause was dehydration, then a sinus infection. But the double vision and headaches didn't go away, so Chris had an MRI that revealed an orange-sized tumor on his temporal lobe.

He was diagnosed with glioblastoma multiforme, which is, in the words of his oncologist Mark Kieran, MD, PhD, "arguably the most malignant tumor in humans." Fortunately, due to the tumor's location, it was able to be removed entirely, and despite a median survival of only seven to nine months, Chris has survived for more than eight years. In that time, he has had two recurrences (and subsequent surgical removals) in the same location and has undergone several rounds of chemotherapy and radiation. And even though the long-term side effects of his treatments have been relatively

Doctors today use three main tools in their fight against cancer: surgery, radiation and chemotherapy. The sidebars describe the experiences that Chris Johnson and Mary Coffin have had with those treatments.



Surgery

Chris has undergone three surgeries to remove the original tumor and two recurrences. The third surgery was done with intraoperative MRI (see page 18). Chris is now missing about a quarter of his brain.

Mary had one surgery to remove the brain tumor and a biopsy of her spinal tumor.



“I have a lot of faith that things will go well. I told my mother once that I wouldn’t die from cancer.”

Despite being diagnosed with a brain tumor eight years ago and having two recurrences, Chris Johnson has survived with few major side effects. He is currently at St. Anselm College in Manchester, N.H., where he is studying criminal justice in the hope of being a prosecutor and, eventually, a judge. He meets regularly with Tom Hammond (left), his senior advisor and Tony Smith (center), his senior seminar professor, to discuss his future.

His oncologist, Mark Kieran says, “We wish we knew exactly what it was about Chris’s tumor that made it stop so we could do it more often. He will teach us things that we’re still trying to learn how to ask. There is a way to stop these tumors, we just haven’t figured out how yet.”



minor compared to what many kids face, he still has suffered seizures, loss of peripheral vision, and has some difficulty processing information.

The same summer Chris was diagnosed, an 8-year-old New Hampshire girl named Mary Coffin also started having vision problems in her right eye. Her optometrist diagnosed her with lazy eye, but when patching didn’t improve Mary’s vision, she had an MRI that revealed a tumor on her optic chiasm.

She was diagnosed with an astrocytoma, which is a less aggressive version of Chris’s disease. Surgeons couldn’t remove the entire tumor because doing so would have caused Mary to go blind, but stereotactic radiation was effective in stabilizing the disease for nearly five years. In 1999, Mary’s tumor not only came back, but spread to her spine. Further treatment stabilized the disease, but in the spring of 2001, the tumor in her spine progressed and caused so much damage that Mary became paraplegic.

In an attempt to stop the tumor growth, doctors put Mary on a new type of chemotherapy that has been successful in slowing some forms of leukemia. The initial results were promising, as the tumor shrank significantly over the next three months and the pain she had been experiencing subsided. But in January 2002, the tumor returned and Mary went back on chemotherapy.

Scott Pomeroy, MD, PhD, director of Neuro-Oncology at Children’s, has treated both patients, and struggles with the difficulties he and others face when caring for

children with brain tumors. “We have had some success with both Chris and Mary. They’re both fighters with tumors we’ve been able to treat, but our biggest frustration is the patients we don’t have an impact on. We can’t push the treatments further, and barring some gigantic breakthrough, there doesn’t seem to be a solution to the problem.”

Kieran, who is director of Pediatric Neuro-Oncology at Dana-Farber/Children’s Hospital Cancer Care (DF/CHCC), puts it another way. “For 30 years we’ve thought we were just around the corner from a cure, but cancer has taught us many times that it’s a much tougher disease than we ever guessed.”

Target acquired

Despite these difficulties, doctors and researchers at Children’s and its partner hospitals are working feverishly to refine current brain tumor treatments, and point to targeted therapies as the best and safest options. The term “targeted therapies” doesn’t refer to a specific treatment, but rather a way of going about treatment in general. In surgery, taking out the whole mass is easier if its exact size has been established. In radiation, beams can be made smaller and more accurate so they are pointed only at the tumor. And in looking for innovative new treatments, target only what’s wrong with the cancer cells rather than poisoning everything in the hope of killing the tumor.

Radiation

After his original diagnosis, Chris had six weeks of radiation, including double sessions during the final two weeks. He also has had 70 total brachytherapy seeds implanted over two surgeries, and had a stereotactic blast, which is a high dose of radiation delivered all at once. To insure accuracy, an aluminum halo is screwed into the patient’s skull and the halo is secured to the radiation table.

Mary had six weeks of stereotactic radiation after her original diagnosis in 1994. Since her tumor relapsed, she has had radiation to her brain and spine.

One targeted therapy that has been successful in surgery is intraoperative MRI, a relatively new technology that helps surgeons remove brain tumors without taking out healthy areas of the brain. The system puts the operating table and surgeons between two large, doughnut-shaped MRI scanners that provide up-to-the-second images of a patient's brain tumor during the operation. Peter Black, MD, PhD, neurosurgeon-in-chief at both Children's and Brigham and Women's Hospital, uses the system often and knows its benefits. "Intraoperative imaging is a quantum leap for us because we can make a three-dimensional reconstruction of the tumor that shows us exactly where and how big it is," he says. "Before this advance, we often didn't know we were missing some of the tumor, so there's no question this technology helps surgeons be more precise and accurate."

Black knows it is only the first step. "New technology like this makes you think about how you can do things less invasively and with less injury," says Black. "New and potentially important treatments come from being able to image the target exactly and remove it cleanly."

Karen Marcus, MD, chief of the Division of Radiation Oncology, also has seen the development of targeted therapies in radiation. In fact, she says, the biggest advances in her field have been treatments in which radiation beams are arranged so they match the shape of the tumor. "Instead of the big square radiation fields we used

to deliver," she says, "we use many small beams from different angles that are aimed at one area. That way the total dose around the target is what we want, but the dose to other parts of brain is very limited."

Marcus points to four examples: stereotactic radiotherapy (SRT), which involves the delivery of multiple doses of very focused radiation; stereotactic radiosurgery (SRS), which delivers a single, large dose of focused radiation all at once; intensity modulated radiation therapy (IMRT), where computers deliver radiation so different areas of the tumor get different amounts of radiation based on where the tumor is the most dense; and brachytherapy, a treatment used on tumors that have already been treated with external beam radiation that involves the surgical implantation of radioactive seeds into the tumor. The seeds provide a high dose of radiation to the cancer cells, while the healthy tissue next to the cells gets almost none.

After surgery and radiation, the last of the three traditional cancer treatments is chemotherapy. Its use in brain tumors has become more prominent in the last 15 to 20 years, but varies based on the tumor type. In some tumors it is used to delay radiation until the child is older because chemotherapy causes fewer long-term side effects than radiation. In other tumors it is used intensively to treat the tumor, and in still others it has a very limited role. Many clinicians believe that if genetic profiling of tumors



Chemotherapy

Mary has undergone five different types of chemotherapy, including the traditional mix of vincristine and carboplatin, after her recurrence in 1999. She was also on Gleevec, a next-generation chemo that has shown success in treating some forms of cancer.

Chris underwent 11 months of chemotherapy immediately following his diagnosis and first surgery.

"I haven't put my health aside or pretended nothing is happening. I've just tried to be a kid and have fun with my friends."

Sixteen-year-old Mary Coffin has made the honor roll throughout her eight-year illness and was president of the student council at her middle school in Henniker, N.H. Coming from a small town has helped Mary share her battle with many of those close to her. She's been friends with Drew Ellis (left) since kindergarten, and other classmates have gone to radiation treatments with her over the years. Last summer, she went to a Red Sox game with Drew, her mother Wanda, and other patients from Dana-Farber/Children's Hospital cancer care.

Mary recently took up impressionist painting and is writing her life story.



(discussed below) can be used to identify which tumors will respond to traditional chemotherapy and surgery alone, the role of harmful radiation therapy can be reduced or even eliminated in the treatment of some tumors.

A new tool

As both a clinician and researcher, Pomeroy has a unique perspective on what it may finally take to stop cancer in general and brain tumors specifically. “The future of treatment lies in understanding the biology of tumors and attacking what’s causing the cancer,” he says.

With that in mind, he has worked closely with Todd Golub, MD, assistant in Medicine at Children’s and an oncologist at the Dana-Farber Cancer Institute, on a technique Golub has revolutionized called microarray gene expression profiling. Spurred on by the unlocking of the human genome, the process uses computers to measure the RNA in tissue. RNA is turned into the proteins that build the body’s cells. From this, scientists hope to identify which proteins are guiding the growth of tumors so they can stop the development of those proteins and, hopefully, the tumor.

Golub envisions this technology giving oncologists around the world a standard, objective set of criteria for diagnosing cancer; one that moves away from the current system of classifying a tumor based on its tissue of origin and how its cells look under a microscope.



One early example of the technology’s potential comes from Golub and Pomeroy, who recently published a paper in the journal *Nature* detailing how they categorized different types of medulloblastomas (a common brain tumor in children) based on their genetic signatures. This then allowed them to determine at diagnosis which tumors would be aggressive and which would grow more slowly. While they haven’t used this information in a clinical setting yet, they hope to do so in the next five years. They plan to tailor treatment regimens so patients with less aggressive tumors can be treated with lower doses of chemotherapy and radiation, thus saving them from the side effects of treatments they don’t need.

The next goal for gene profiling is to use the information to develop, in Golub’s terms, “molecularly targeted therapies that go after what’s broken in the cancer cell, not with an atom bomb, but with a magic bullet.” As an example, he points to Gleevec, a drug developed without the benefit of gene profiling, but one that has been successful in treating acute myeloid leukemia (AML). It specifically targets the molecular problem that causes it, and has been shown to slow the progress of AML while causing very few side effects.

Golub is encouraged by what he sees with Gleevec. “It shows that different cancers have Achilles’ heels, and by using gene expression profiling to understand what is causing a specific disease on the genetic level, we should be able to target its weakness effectively and cause fewer side effects. Now we need to develop such drugs for brain tumors.”

Pomeroy believes gene expression profiling, combined with other techniques that lead to a molecular understanding of cancer, may be the breakthrough that has eluded doctors for generations. “I can’t think of another way that’s more likely to succeed. Going step by step and understanding exactly what the problem is and then specifically dealing with that problem is the way to go,” he says. “I have a lot of hope. I think we’re heading in the right direction, and that it’s only a matter of time before this will pay off.”

—Matthew Cyr

Editor’s note: In November 2002, Mary Coffin lost her eight year battle with cancer. Children’s Hospital extends its heartfelt condolences to the Coffin family.

For more information on supporting the Neurology Leadership Fund, which supports research in pediatric brain tumors and neurologic disorders, contact Donna Richardson in the Children’s Hospital Trust at (617) 355-2061 or at donna.richardson@chtrust.org.

In addition to gene expression profiling, there are a number of other promising areas in cancer study and treatment.



Proteomics Measuring proteins (which decide what functions a cell can perform) in a tumor. Cancer typically mutates proteins.

Genomics Identifying abnormal DNA sequences that may be responsible for mutant proteins. Helps identify inherited genes that predispose someone to cancer.

Antiangiogenic therapies Using naturally occurring or chemical substances to cut off a tumor’s blood supply.

Gene therapy Introducing a foreign gene into the body to correct a defective gene, stimulate the immune system or make the body resistant to chemo so higher doses can be given.

Immunotherapy Stimulating the immune system so the body’s natural defenses will recognize and attack cancer cells.

Small molecule inhibitors Drugs that block proteins’ signaling components to keep them from triggering cancer’s out-of-control cell division.