

The Science of Survival

No magic bullet exists to cure the brain tumors known as gliomas, but scientists continue to advance diagnosis and treatment.

BY STEPHANIE STEPHENS

As Jana Kosiba was being prepped for her second brain surgery, in March 2010, she told her surgeon, “Oh, don’t worry. I’m not scared. I know everything’s going to be okay.” Never a complainer, she did admit later that “the second surgery was a lot more painful than the first.”

The contagiously upbeat Kosiba, age 46 of Everett, WA, was diagnosed with her first brain tumor in March 1999—a malignant glioma, which is a tumor that starts in the brain or spinal cord. It is called a glioma because it arises from “glial” cells, which help provide support and protection for nerve cells that transmit signals (neurons). Her glioma is called an oligodendroglioma because it arises from oligodendrocyte cells in the brain.

Kosiba knew she had to see a doctor when she fell down

after returning home from an enjoyable day of shopping from what turned out to be a seizure. (She had no history of seizures.) It was the start of a journey that finds Kosiba unwavering as she stands up to her unwelcome visitor.

“At first, after surgery, you think you’re cured,” says Kosiba, “and then you realize, ‘Oh right, this is a *managed* disease.’” To manage hers, Kosiba has undergone surgery as well as standard radiation and chemotherapy treatments.

A COMPREHENSIVE APPROACH

All are part of a comprehensive approach managed by her neuro-oncologist, Lynne P. Taylor, M.D., Fellow of the American Academy of Neurology (AAN) and director of neuro-oncology at Virginia Mason Medical Center in Seattle, WA. A neuro-

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oncologist is a neurologist who specializes in the treatment of cancer and tumors affecting the brain and spinal cord.

Kosiba’s drug regimen includes an antidepressant (for depression unrelated to her brain tumor) plus an antiseizure medication to treat her disease-related seizures. She also takes a number of supplements that contribute, says Dr. Taylor, to her overall well-being: a multivitamin, fish oil, calcium and magnesium, vitamin D, and melatonin.

In addition, naturopathic physicians from nearby Bastyr University—who practice primary care through the use of natural therapies—confer with Dr. Taylor for Kosiba’s complementary and alternative medicine (CAM) treatments, including acupuncture, oncology massage, and a combination of Chinese herbs. Since Kosiba began incorporating CAM, in March 2011, she says it has helped relieve her chemotherapy symptoms: constipation, headache, fatigue, leg cramps, and hot flashes.

“I’m supportive of almost any technique my patients can use to gain control over their disease, and many of my patients use CAM,” Dr. Taylor says.

The National Center for CAM, which is part of the National Institutes of Health, reports that as many as 54 percent of all cancer patients incorporate CAM. Doctors and patients should have an open and critical dialogue about the use of CAM, according to a study published in the December 14, 2010, issue of the AAN’s medical journal, *Neurology*. In fact, many doctors feel that patient engagement in a treatment plan—whether it incorporates CAM or not—can make the difference between thriving and just surviving.

Who Is at Increased Risk for Brain Tumor?

According to the American Brain Tumor Association (abta.org), the following groups may be at a higher than average risk for the type of brain tumors known as gliomas:

- ▶ People who have had ionizing radiation to the head, such as for a tumor during childhood. “It’s very rare,” says Dr. Dietrich. “Keep in mind, though, that when you apply radiation, there could be a potential risk down the road.”
- ▶ Individuals with rare syndromes such as neurofibromatosis.
- ▶ First degree relatives (siblings, parents, and children) of glioma patients. In fact, approximately 5 to 10 percent of gliomas may be related to inherited gene mutations.

SYMPTOMS OF BRAIN TUMOR

Brain tumor symptoms are often similar, even if tumors aren’t, says neuro-oncologist Jörg Dietrich, M.D., Ph.D., of the Cancer Center of Massachusetts General Hospital in Boston and an American Academy of Neurology Clinical Research Fellow. In addition, brain tumor symptoms can resemble those of other diseases. According to Dr. Dietrich, the most common symptoms of brain tumor are headaches, seizures, personality changes, “focal deficits,” and “mass effect.”

Headaches, which may be in a specific area or felt all over, are a typical symptom of brain tumor. Sometimes they are associated with nausea and vomiting. “Headaches may be a concerning symptom if they’re severe and occur in a patient who has never had a headache before,” Dr. Dietrich says.

Seizures are often a “wake-up call” for people like Kosiba who have not experienced them before. Seizures occur in up to half of oligodendroglioma patients and can happen with all types of brain tumors.

Personality changes are another common brain tumor symptom. If someone’s character and personality changes over the course of weeks or months—for example, he or she becomes more irritable, aggressive, or withdrawn from society—a tumor could be to blame.

Some people also experience a “focal deficit,” which is a problem in the brain or spinal cord that affects a specific location in the body. A focal deficit might cause weakness or numbness in one arm or leg or on one side of the body. “While these symptoms may also be seen in stroke patients, focal deficits in cancer patients usually develop over weeks and months,” Dr. Dietrich says. In the case of stroke, the focal deficits occur suddenly.

Another sign of a brain tumor is increased pressure inside the skull (called “mass effect”), which is usually due to tumor growth. This common symptom of brain tumor can cause vision problems, nausea, drowsiness, or any of the other symptoms noted above. The intruding tumor tissue expands spatially, displacing or pushing away the normal brain tissue within confined space in the skull.

While the symptoms are often recognizable, the causes of brain tumor remain virtually unknown. “For many cancer types—such as lung, colon, and pancreatic—clear risk factors exist such as smoking, alcohol, or specific diets,” Dr. Dietrich says. “Nothing like this exists in the brain cancer world. These tumors, in most cases, come ‘out of the blue.’”

TUMOR TYPES

One in every 100 tumors diagnosed in the U. S. annually is a brain tumor, and more than 120 types of brain tumor have been identified. An estimated 64,530 new cases of primary



SMELL THE FLOWERS

Jana Kosiba and her husband, Paul Kosiba. She maintains a positive attitude in the midst of brain-tumor treatment.

brain tumors—those that originate in the brain—are expected to be diagnosed in the U.S. this year.

A brain tumor is a mass of abnormal cells growing and multiplying in the brain. Two common kinds of brain tumors are astrocytomas and oligodendrogliomas. Both are types of gliomas. These primary brain tumors originate in glia, sometimes described as the “gluey” supportive brain tissue that provides structure and function for neurons. Primary brain tumors rarely spread (metastasize) outside the brain and spinal cord.

Astrocytomas are the most common type of gliomas, and the most aggressive astrocytomas are glioblastomas. They occur more frequently in men than women and in older adults.

Oligodendrogliomas are slow-growing and usually form in middle-aged patients like Kosiba. In her case, a chromosomal abnormality in the tumor works in her favor. “It’s more responsive to chemotherapy,” Dr. Taylor says.

Tumors are labeled benign or malignant (cancerous). According to the American Brain Tumor Association (ABTA), a benign brain tumor is slow-growing, has distinct boundaries, and rarely spreads. Surgery alone may be an effective treatment; but if the tumor is located in an area of the brain that controls vital functions, surgery can be life-threatening. On the other hand, malignant brain tumors—which are invasive and faster-growing than benign tumors—usually are life-threatening.

However, “all tumors are what doctors call ‘bad actors,’” says neuro-oncologist Benjamin W. Purow, M.D., of the University of Virginia Health System in Charlottesville. “Even benign tumors can be fatal. The brain is high-priced real estate.”

“A brain tumor is about location, location, location,” says Dr. Taylor. “If the tumor is in the dominant hemisphere or has infiltrated ‘the eloquent brain’ that controls speech and motor function, it cannot be treated with surgery.” A person’s dominant hemisphere

is the one most involved in governing certain body functions, such as controlling the dominant arm in skilled movements.

Even if surgery is “successful,” with a tumor removed to within 3 cm of the tumor site, some microscopic tumor is left behind that can return, says Dr. Taylor. “We can’t make it go away forever. When, following surgery, the patient sees her MRI with a big, black hole where the tumor was, that is a macroscopic versus microscopic view. So our goal is for the patient to be a long-term survivor with a high quality of life.”

DIAGNOSIS

Diagnosis begins with a comprehensive neurologic exam. With enough evidence to move forward, such as abnormalities in movement, gaze, hearing, balance, or touch, a scan such as MRI or CT follows.

“However, just because we see a mass on a scan, doesn’t mean it’s a tumor,” says Susan F. Chang, M.D., director of the Division of Neuro-Oncology at the University of California, San Francisco (UCSF). “Even diagnosis can be challenging,” she says.

Once a diagnosis is made, specialists like her ask two crucial questions: What kind of tumor is it? Then—following surgery—how much tumor remains?

When possible, a tissue sample (biopsy) is taken for microscopic analysis by neuropathologists. They will identify or name the tumor based on where it originated, its pattern of growth, and whether or not it is cancerous.

The tumor is graded on its tendency to spread or infiltrate, growth rate, and similarity to normal cells, using criteria for gliomas from the World Health Organization. (See box, “Tumor Grades.”)

TREATMENT

Next, a multidisciplinary team determines a treatment course. At major medical centers such as teaching hospitals, that team may include a neuro-oncologist, neuroradiologist (who uses x-rays and other scanning devices for diagnosis and treatment of nervous system diseases), neurosurgeon, and radiation oncologist (who specializes in the use of radiation therapy to treat cancer).

Surgery is the first line of defense for an accessible tumor, to reduce the tumor’s volume and often decrease pressure. Risks for any general surgery apply to brain surgery: infection, clotting, bleeding, and unstable blood pressure.

Each patient and tumor is treated individually, and not all patients require all three modalities (surgery, radiation therapy, and chemotherapy). In order to slow tumor growth and improve symptoms, radiation therapy and chemotherapy may be started in some patients within two to four weeks following surgery. Radiation to kill cells or stunt tumor growth is given for brief peri-

ods, usually five days weekly for four to six weeks, along with chemotherapy for the same period.

Chemotherapy, used in conjunction with radiation, attacks dangerous, dividing cells. The oral medication temozolomide (Temodar) “made a major impact on our field,” Dr. Purow says. “It is well-tolerated and effective, and people generally don’t lose hair or become terribly nauseated from it. Patients may be able to keep working while taking it as well. Blood counts do usually drop somewhat with temozolomide, especially platelets, but overall less than with most chemotherapies.”

Temozolomide, which is Kosiba’s chemotherapy, is typically used for all Grade 3 and 4 gliomas and may also “sensitize” patients to radiation, making it more effective, Dr. Purow says. After radiation, it is usually prescribed alone for six months to one year.

Gliadel, a chemo-loaded, implantable “wafer,” gained initial FDA approval in early 2003, but it is not widely used, Dr. Purow says. Following tumor removal, the wafers are inserted into the area where the surgery was performed.

FDA-approved early this spring to curb tumor growth, the NovoTTF-100A System generates changing electrical fields through the scalp from a battery pack carried by the patient. “This showed comparable outcomes to patients receiving chemo,” says Dr. Purow.

HOPE, HELP ON THE HORIZON

“We are extending lives, giving patients access and attention they deserve and need. There’s so much value and satisfaction in that,” Dr. Purow says.

Though no magic bullet can “cure” a brain tumor yet, science incrementally beefs up a patient’s “survival advantage,” adding more ammunition to the treatment arsenal and possibly prolonging life.

“We all want the key to match the lock—that is, to find drugs that are the perfect fit for an individual patient,” says Dr. Dietrich.

Drug therapy to quash lethal, persistent tumors continues as a high priority in nationwide clinical trials.

“Even with advances in treatment, given the nature of tumors, we’re still challenged when they ‘break through,’” says Dr. Chang. “How can tumors like glioblastomas continue to grow despite radiation and chemotherapy, and be so drug resistant? Understanding the uniqueness of an individual patient’s tumor and tailoring treatment may allow us, in the future, to kill every last infiltrating cell,” she says.

The identification of genetic differences in tumor cells is one way to tailor treatment. “A tumor develops a distinct genetic signature, its own world—a ‘micro-environment,’” Dr. Dietrich says.

Tumor Grades

Doctors group brain tumors by grade. The grade of a tumor refers to the way the cells look under a microscope.

- ▶ **GRADE I:** The tissue is benign. The cells look nearly like normal brain cells, and they grow slowly.
- ▶ **GRADE II:** The tissue is malignant. The cells look less like normal cells than do the cells in a Grade I tumor.
- ▶ **GRADE III:** The malignant tissue has cells that look very different from normal cells. The abnormal cells are actively growing (anaplastic).
- ▶ **GRADE IV:** The malignant tissue has cells that look most abnormal and tend to grow quickly.

Cells from low-grade tumors (grades I and II) look more normal and generally grow more slowly than cells from high-grade tumors (grades III and IV).

Over time, a low-grade tumor may become a high-grade tumor. However, the change to a high-grade tumor happens more often among adults than children.

Source: National Cancer Institute at the National Institutes of Health: cancer.gov/cancertopics/wyntk/brain/page3

Scientists think the micro-environment has substantial influence on the biology of the tumor.

Some of the promising avenues for research include the following:

Signaling pathways and molecular targeted cancer therapies:

“Tumors depend upon signaling pathways to grow, divide, and form blood vessels,” says Dr. Chang. Normal proteins and enzymes in genes communicate via these signaling pathways. Scientists know that abnormal signaling in individual molecules can encourage tumor formation and growth, and they seek to “block” the process.

Approved for patients with recurrent glioblastoma, bevacizumab (Avastin) targets new blood vessels “feeding” tumors like glioblastomas. Avastin is administered intravenously every two to three weeks and usually combined with other chemotherapy.

“Almost everyone with high-grade glioma gets this therapy when previous treatments have failed,” Dr. Purow says.

Stem cells: In late June, a Johns Hopkins Medicine study announced that in young adult mice, a lone brain stem cell is capable not only of replacing itself and giving rise to specialized neurons and glia, but also of generating new brain stem cells.

Researchers believe targeting cancer stem cells in brain tumors may also reduce blood supply that feeds a growing tumor, thus reducing tumor growth.

Biomarkers: Cancerous cells release unique proteins and other molecules into the body, which scientists detect and use to speed diagnosis and treatment. Analyzed from spinal fluid or blood, they can indicate early on if a patient is responding to treatment. Researchers are investigating whether different biomarkers exist in different tumors.

Immunotherapy and vaccines: “Our own immune system is always actively engaged in the fight against a growing brain tumor,”

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—SUSAN F. CHANG, M.D., UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

says Dr. Dietrich. A patient’s immune system can be engaged to kill proteins contained in cancer cells.

“Immunotherapy performs ‘surveillance,’ then locates and eliminates tumor cells early and safely,” Dr. Chang says, citing documented immunotherapy success in treating melanoma and kidney cell cancer.

Separate immunotherapy trials are being conducted at UCSF and Duke University. A vaccine developed at Duke “educates the immune system to produce antibodies that...attack the tumor very specifically,” the medical center’s Dr. John Sampson told CBS News last fall.

Convection-enhanced drug delivery: Chemotherapy can be delivered in higher concentrations from a pressure pump directly to brain tissue, versus injection into a vein. This delivery also circumvents the protective blood-brain barrier, “that very tight junction between cells that prevents chemicals from entering the brain,” says Dr. Chang. Normally, the barrier is a good thing, but

not when a needed chemo drug must cross it.

With any new therapy, scientists proceed with caution, Dr. Chang says. “Safety is our top priority. We don’t want to launch into something and later say, ‘This wasn’t a good thing to do.’”

Relying on traditional therapies and CAM, Jana Kosiba forges ahead, educating other patients that with an integrated, comprehensive plan of attack, “there’s no need to suffer uncomfortable symptoms.”

Her goals—and she has many—include more physical activity. Brain cancer patients who are able to exercise live significantly longer than sedentary patients, scientists at the Duke Cancer Institute report.

“Now, I only walk my dog. I need to do more,” Kosiba says. Those who know her have no doubt she will. NN



For more information on brain tumor, see **RESOURCE CENTRAL** on page 36.

What to Ask the Doctor

Drs. Jörg Dietrich, Benjamin Purow, and Lynne Taylor created the following list of questions:

What does it mean to be a long-term survivor?

Let’s talk about whether duration or quality of life should be more important to me...

What would you do if this was happening to you or a family member?

What is the name of my tumor? Its grade?

My treatment options?

How can I incorporate complementary and alternative medicine into my plan?

Should I be in a clinical trial? How do I do this?

How can I reduce my worry and stress, especially before each MRI?

What is the toxicity of treatment? The side effects?

What complications could occur, unrelated to treatment?

(“For example, neurologic and neurosurgical patients are prone to blood clots or deep vein thrombosis because they are immobile or because their blood is more likely to coagulate,” says Dr. Dietrich.)

How do I handle diarrhea, vomiting, and fatigue initially? Then, how should I manage the long-term toxicity of chemotherapy?

How do I control seizures?

What cognitive changes should I expect?

How important are diet and nutrition? (“Tumors form less frequently in a lean body,” says Dr. Dietrich.)

How many brain tumor patients do you see in a year? (“A number from 300 to 500 is great,” says Dr. Taylor.)

How many craniotomies do you do annually?

(During this procedure, the surgeon creates a hole in the skull and removes a piece, called a bone flap. “A neurosurgeon should say ‘more than 50,’” says Dr. Taylor.)

When should I call you and when not?

Should I travel to a big medical facility?

Can I travel? (“One of my patients asked, ‘Can I bungee jump?’” Dr. Dietrich recalls.)

What’s my prognosis?

Finally, they offer this advice:

“Take an active role,” Dr. Dietrich advises.

“Know that exciting developments are in the pipeline,” says Dr. Purow.

“Remember: you can co-exist with this tumor peacefully,” says Dr. Taylor.