The Meningioma Initiative

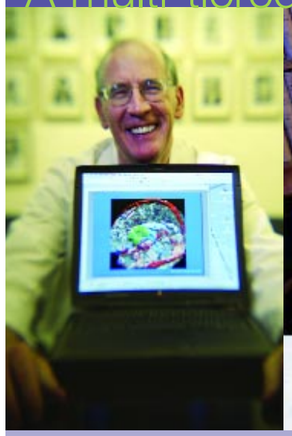
BWH makes headway against a brain tumor long neglected by research.

Some neurologists and neurosurgeons have an adage: There is no such thing as a benign brain tumor. Meningiomas, typically noncancerous tumors of the membranes lining the brain and spinal cord, often serve as their case in point. So subtle are meningiomas' warning signs that these tumors may go unnoticed until they are larger than a golf ball. At this point, they can cause such a broad array of symptoms—from memory loss to difficulty speaking, unsteadiness, headache, spasms of the facial muscles, seizures or loss of hearing, vision or smell—that they evade a timely diagnosis, deftly mimicking any number of maladies.

Niki Pantazis

Niki Pantazis was lucky. She learned of her tumor by accident 11 years ago, when a blood test to see if she was entering menopause showed high levels of the hormone prolactin, which can indicate a tumor of the pituitary gland. Magnetic resonance imaging (MRI) instead revealed a two-inch growth near the top of her brain's left hemisphere; the large vein to which it was attached, she was told, would make removal

A multi-tiered attack plan



PETER BLACK, MD, PHD, leads the Meningioma Initiative at BWH. A pioneering researcher and a veteran of more than 3,000 brain surgeries, Black uses advanced imaging software as a guide, excising many tumors formerly considered inoperable. That software was developed at BWH by **RON KIKINIS, MD,** and his colleagues in the Surgical Planning Laboratory.

By combining clinical, epidemiological and biological data on patients with meningioma, neurosurgeon and biostatistician **ELIZABETH CLAUS, MD, PHD,** is looking for risk factors for the tumor in hope of identifying individuals who might benefit from specific treatments or preventive measures.

Behind Neurosurgical Laboratory Associate Director **RONA CARROLL, PHD** (seated) and research technician **THERESA CARGIOLI** is an image of encapsulated cells that they say hold potential for suppressing brain tumors. The cells secrete endostatin, an agent that cuts off tumors' supply of oxygen and nutrients by shrinking their blood-vessel network.

When surgery is impossible or a tumor cannot be completely removed, radiation therapy is in order. Radiation oncologist **NAREN RAMAKRISHNA, MD, PHD,** uses a highly focused treatment pioneered at BWH called fractionated stereotactic radiotherapy to shrink tumors while sparing normal brain cells. Weak radiation beams pass harmlessly through brain tissue from many angles, converging upon the tumor in concentrations capable of destroying abnormal cells.

difficult. Eager for a second opinion, Pantazis sought out Peter Black, MD, PhD, chief neurosurgeon at Brigham and Women's and Children's hospitals, who urged her to have it out before it did any lasting damage. But as a single mother of two teenage girls, Pantazis chose to take a wait-and-see approach.

For a decade, Pantazis remained asymptomatic, keeping the secret from her younger daughter, Maria, and soft-pedaling her fears when the older one, Joanna, started asking questions. But in January of 2002, when another MRI showed a significant increase in her tumor's size, Pantazis could no longer deny that something had to be done, and she returned to BWH for her operation. "I'd done my homework," she says, "and found that Dr. Black was the best we have."

They scheduled the surgery for 10 days after Maria's college graduation. "I was devastated," says Pantazis, who agonized over the worst-case scenario, despite Black's reassurances. "I drew up my will. I wanted the girls taken care of."

Pantazis' fears have long since been dispelled.

PANTAZIS, who was 48 at the time of her diagnosis, fits the profile of a typical meningioma patient. The tumor strikes women twice as often as men, and no one is sure why (see sidebar on page 19). The most common age of onset is between 40 and 70, though meningiomas also strike younger adults, teens and children. And Pantazis' tumor followed an unpredictable course, as they so often do: Though two surgeons urged her to have it removed, she managed to live with it for 11 years, symptom-free.

Finally, like so many meningioma patients, "Niki was terrified of the surgery," says Peter Black. "People think 'brain surgery' and they assume it will be awful, that they'll wake up paralyzed. But generally, they're pleased with the outcome."

Meningiomas account for an estimated 27 percent of all primary brain tumors—that is, tumors that originate in brain tissue. According to Black, more than 95 percent are noncancerous, with a five-year survival rate of 95 percent. The chances a tumor will recur depend on how completely it can be removed, as well as on certain biological attributes that are not well understood. Morbidity rates vary with a tumor's location and the type of surgery. Unfortunately, the lasting consequences of meningiomas can include hearing loss, weakness of the facial muscles, blindness and stroke.

But for Pantazis, recovery was complete and relatively quick. "The first time I went out," she says, "it took me half an hour to walk from one side of my house to the other, and I cried and cried. But by the end of the third week I was walking three miles. I was so happy to be alive. The pathology report showed that my tumor had just begun to turn cancerous."

THOUGH FIRST DESCRIBED in 1614, meningioma was not classified as a distinct category of tumor until 1938 by the legendary father of neurosurgery, Harvey Cushing, MD, who for 20 years served as surgeon-in-chief at the Peter Bent Brigham Hospital, a forerunner of today's BWH. Meningiomas affect 2.6 of every 100,000 Americans, not by invading brain tissue but by pushing it aside as they enlarge.

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>
> —Peter Black, MD, PhD

Although more than six decades have passed since Cushing's time, little is known about these tumors. Until recently, neither hospitals nor state registries tracked their incidence. "Meningioma remains a neglected tumor," Black says, "partly because it is usually benign, partly because there are no advocates for research." Brigham and Women's intends to change that.

"We'd like to fill the void," says Black. "This hospital is ideally suited for a leadership position in trying to understand, treat and prevent meningiomas."

Why? For several reasons. The hospital has advanced neurosurgical capabilities, including image-guided, minimally invasive technologies, advanced brain-function monitoring and neuroanesthesia, and an expert team of neurosurgeons. It is also a pioneer in conformal, or highly focused, radiation therapy, which can be used as an adjunct treatment. And Black—who is also the chief of neurosurgical oncology for the Dana-Farber/Brigham and Women's Cancer Center, a collaboration between BWH and neighboring Dana-Farber Cancer Institute—points out that "the richness of the scientific and educational environment" allows for productive inquiry within realms such as gene expression, epidemiology and innovative drug therapies. In 2002, the hospital launched a concerted attack on meningiomas with $5 million from the Brain Science Foundation, founded by one of Black's former patients (see sidebar on page 16).

Several BSF-sponsored initiatives are well under way.

Elizabeth Claus, MD, PhD, a neurosurgeon and biostatistician, is working with Black on a three-tiered pilot study. The first phase entails interviewing patients and healthy subjects to pin down the possible causes of meningiomas. So far, radiation exposure and hormones seem to be the strongest risk factors; others may include genetic predisposition and viral infection. In the second phase, Claus will study tumors' receptivity to the hormones estrogen and progesterone. "Attempts have been made to block estrogen and progesterone receptor molecules on meningiomas," she says, "but they've not been terribly successful. If we can learn more about these receptors and characterize any subtypes, we may be able to figure out which tumors will respond best to receptor-blocking therapies."

The third phase of Claus' research will examine the expression of thousands of genes within a set of meningiomas. "We want to see how certain genes relate to a patient's prognosis or to a tumor's clinical characteristics, such as how fast it's growing," Claus says. "Ultimately, we hope to determine which treatment will most benefit a particular patient, given his or her tumor's genetic makeup."

Meanwhile, Neurosurgical Laboratory Associate Director Rona Carroll, PhD, is developing animal models and cell lines in which to study the disease. "Surgery is effective," she says, "but sometimes tumors, or parts of tumors, are inoperable, and we need to find the best way to treat cells that remain after surgery. Chemotherapy helps, but with any drug the Food and Drug Administration requires animal toxicity and efficacy studies, and until recently meningiomas were tough to grow in mice."

Working with a laboratory in France, Carroll and her colleagues have developed a "knockout mouse," one that's missing two genes whose absence allows meningiomas to take hold more easily. But this mouse model is far from perfect: It can take up to 11 months to develop a meningioma, a fair number of the rodents remain healthy, and some develop other kinds of tumors.

Once Carroll comes up with a reliable model, she will study drugs and drug-delivery systems that target meningiomas. In mice, for example, the Alzet mini-pump channels medicine directly into the brain through an implanted tube running from a reservoir. Other promising delivery systems include nanoparticles, tiny cage-like polymers that are impregnated with new compounds such as PEX and implanted into the tumor site. First isolated in Black's lab, PEX has been shown in mice to keep virulent brain malignancies called gliomas from recurring by squelching the blood vessels that nourish them as they grow.

"Ultimately, we hope to determine which treatment will most benefit a particular patient."

—Elizabeth Claus, MD, PhD

Until questions surrounding which drugs to use and how best to deliver them are sorted out, surgery remains the treatment of choice, provided it can be done safely and completely. If some part of a tumor proves inoperable, however, radiation therapy may be used to control its growth. More than 10 years ago, BWH neurosurgeons and radiation oncologists showed that a highly focused form of radiotherapy known as stereotactic radiosurgery could help meet that challenge. Today, Naren Ramakrishna, MD, PhD, director of the BWH Adult Central Nervous System Radiotherapy Program, is comparing the results of conventional surgery, stereotactic radiosurgery, and a multi-dose variant of the latter called fractionated stereotactic radiotherapy on tumors in various locations within the brain. He hopes to better understand these targeted treatments' impact on tumor control as well as their potential complications.

An entrepreneurial approach

How one patient's strategic plan is driving research forward

In the summer of 1997, doctors told Steven Haley he had a brain tumor. "At the time, I was not quite sure of the proper pronunciation of 'meningioma,' how to spell it, what it was," Haley recalls. "I knew virtually nothing." Today, this Internet entrepreneur can rattle off facts and figures about the disease like a resident facing a tough attending physician's cross-examination. The steep incline in Haley's learning curve—and his surprise at realizing how little scientists really know about meningioma—led him and his wife, Kathleen, to establish the Brain Science Foundation, and to make an initial gift of $5 million to support research led by Peter Black, MD, PhD, chairman of Neurosurgery at the Brigham and Women's and Children's hospitals.

"The broad opinion is that not enough is being done to find the causes of meningioma," Haley says. "And without research, promising treatments—and, ultimately, the prevention of tumors—will not come anytime soon. We said, 'Let's expedite the whole process of exploration, research, diagnostics, treatment and education.'"

As a nonprofit supporting organization—that is, one whose funds are dedicated solely to a particular cause—the Brain Science Foundation and organizations like it take what Haley calls "an entrepreneurial approach to gift-giving that is project- and milestone-oriented. It's methodical and systematic. It has timelines, it has identified resources, and it aims to produce results."

A frustration for Black, a world leader in neurosurgery, has been the paucity of government funding for meningiomas and other important areas of neuroscience. "A disproportionate amount of money goes to studying degenerative diseases—Huntington's, Parkinson's, ALS—and certain kinds of stroke and epilepsy," he says. "But there's a whole world of problems not covered: head and spinal-cord trauma, the cognitive impairment resulting from minor head trauma, hydrocephalus and especially brain tumors.

"Brain tumors are an orphan disease," he continues, "long neglected by oncologists and neurologists. Meningiomas are an extension of a larger problem that isn't rare and can be quite devastating, yet lacks a place in the traditional scientific fabric."

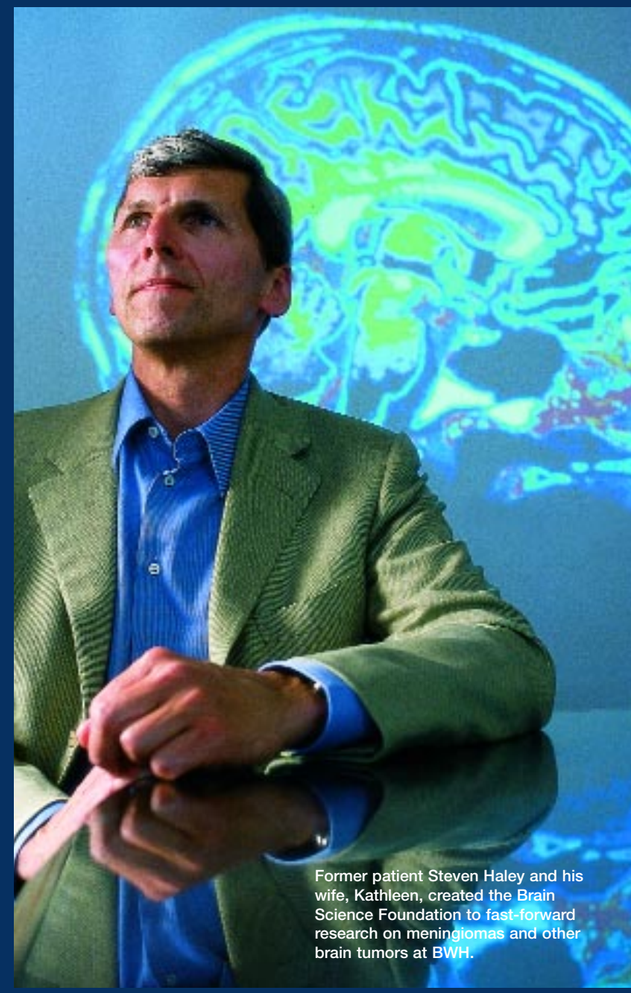
The Brain Science Foundation aims to change that by tackling research, education and patient care simultaneously.

"Seeing patients in a crowded, understaffed space, when they're on pins and needles thinking this is a life-or-death situation, is not conducive to a positive outlook," says Haley, who knows whereof he speaks. The BSF, in cooperation with BWH, has provided funding for the remodeling of the neurosurgical patient waiting area. This fall, the outpatient facility will feature computers with desktop information on brain tumors and Internet access, a rack full of educational materials, magazines and videotapes, comfortable seating and a refreshment station. A newly hired patient-care coordinator will walk patients through their appointments.

The effort will help those already diagnosed feel more at ease. But crucial to seeing fewer diagnoses in the future is the BSF's plan to create fellowships for physician-researchers in training at the hospital, endow the Steven R. and Kathleen P. Haley Professorship in Neurosurgery at BWH and Harvard Medical School, and give research a big push forward.

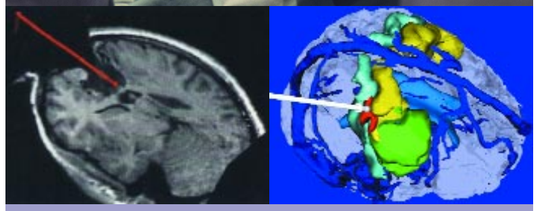
"Until now, meningioma research hasn't been a sexy field," Haley says. "We want to get a buzz going around it, create interest so that more papers will get published, more research will be initiated, and major grant money will begin to come in. Our goals are to find better ways to diagnose, treat and prevent meningiomas. In the next 10 years, I hope we will have helped to get there."

For more information, log onto www.brighamandwomens.org/neurosurgery/meningioma/meningiomafacts.asp and www.brainsciencefoundation.org/. ◆



Former patient Steven Haley and his wife, Kathleen, created the Brain Science Foundation to fast-forward research on meningiomas and other brain tumors at BWH.

Intraoperative MRI



Inside the world's first Intraoperative MRI Suite, BWH surgeons stand inside an MRI machine, their procedures guided by a series of two-dimensional images (above, left) taken along any plane, as indicated by the surgeon's pointer. A light-emitting diode on the pointer communicates with a computer, which captures the images in real time on a screen above the surgeon's head. Software developed in the BWH Surgical Planning Laboratory renders the brain in three dimensions (above, right).

"Two decades ago," he says, "our equipment was irradiating not just the tumor, but two or three centimeters of brain around the tumor. Now, with stereotactic radiosurgery, we've shaved that margin down to a couple of millimeters. The benefit is obvious: we're irradiating much less normal brain. But we want to get a better handle on the long-term advantages as well as the side effects of these new treatment technologies."

NEUROSURGEONS AT BWH need no reassurances that new technologies have enhanced their ability to remove meningiomas and other brain tumors, even from patients whose tumors were judged inoperable elsewhere. Because a brain tumor can look like healthy tissue to the naked eye, physicians must rely on MR scans to spot it. In the hospital's basement sits the world's first open, "intraoperative" MR scanner, invented in the early 1990s by Ferenc Jolesz, MD, director of MRI and Image-guided Therapy, and collaborators at BWH and G.E. Medical Systems. It is one of only 16 such machines in the world.

What distinguishes this operating room from others containing MR scanners is that the patient is not slid in and out of the machine and imaged between bouts of surgery. Instead, the surgeon stands between a "double donut" of magnets, operating while the scanner takes cross-sectional pictures of the patient's brain in real time. These images are beamed onto a small screen above the operating field.

Just outside the operating room window, a bank of high-tech computers allows a radiologist to control and interpret what the surgeon sees. Scans are constantly updated, since every move the surgeon makes can alter the brain's anatomy.

Speaking by intercom to the radiologist one recent morning, Black aspirates the tumor of a 51-year-old male, asking for directions like a driver navigating by cell phone. "Move toward the cerebellum," the radiologist responds. "Now, slowly go lower. There you are. Superficially you had it all, but there's more deep down below." Each aspiration causes the tumor and surrounding tissue to shift. Further instructions ensue until every last bit of the growth has been extracted, with minimum harm to normal tissue and the smallest possible opening made in the skull.

"The radiologist and MRI act as my eyes, showing me what's left far better than my own eyes could," says Black, smiling broadly as he steps out of the Intraoperative MRI Suite. "For patients once told that their tumors were inoperable, the outlook has never been brighter."◆

A pregnancy in peril

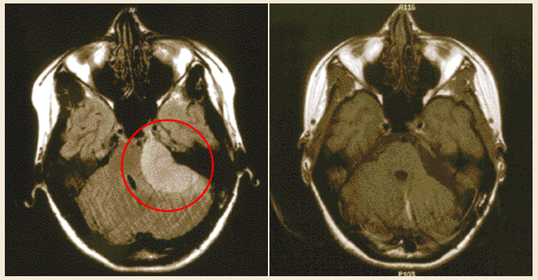
Do hormones fuel tumor growth?

At age 31, Lisa Driscoll began to lose hearing in her left ear, but she was too preoccupied to give it much thought. "I was excited about being pregnant with my first baby," she says. "I had just left my job in law to open a boutique, and we were doing a major house renovation. So I had lots of other stuff to focus on."

When a nurse friend noticed that Driscoll could not make out what she was saying at a dinner party in the summer of 2000, she suggested it was probably just a little waxy buildup. "So I went in," says Driscoll, recalling her clinic visit, "and five hours later they had done umpteen tests. In hindsight I realize it was pretty unusual for them to be clearing their schedules for me right on the spot."

Because of an earlier miscarriage, Driscoll resisted going for magnetic resonance imaging until her third trimester. Even when MRI confirmed what doctors suspected—a tumor, likely a meningioma, impinging on her acoustic nerve—she wanted to wait until the baby was born to have her surgery, despite some memory loss and speech problems.

At Brigham and Women's Hospital, Neurosurgery Chairman Peter Black, MD, PhD, had other ideas. On her first visit to see him, Driscoll recalls, "Dr. Black asked me, 'What are you doing Thursday?'" suggesting that she get to the operating room before the tumor could cause any more damage.



Magnetic resonance imaging is ideal for generating highly detailed, cross-sectional images of soft tissue and bone. The scan of Lisa Driscoll's brain at left reveals a large meningioma (circled in red) that has displaced normal tissue, increasing the pressure within her skull. The scan at right, taken after a 13-hour surgery, shows no sign of tumor.

"Growth during pregnancy is unpredictable," says Black. "Why? I don't think anyone knows."

The research is indeed inconclusive, even contradictory.

Because meningiomas strike women twice as often as men, scientists are looking to hormonal factors to help explain these tumors. Studies show that they can grow more rapidly during pregnancy, and may be associated with the use of hormone replacement therapy following menopause. Women who develop meningiomas appear to be at a heightened risk for breast cancer and vice versa, though so far these tumors do not appear to have mutations in the breast-cancer-related genes known as BRCA1 and BRCA2. Receptors for both estrogen and progesterone appear in some meningiomas, suggesting that these hormones may modify cell growth and differentiation.

On the other hand, meningioma is hardly exclusive to women. And its incidence is much higher in women 50 and over—whose hormone levels have declined precipitously—than in women of child-bearing age. Until more studies are done, such seeming contradictions will remain a mystery.

All of which offers little comfort to women who, like Lisa Driscoll, must make life-or-death decisions for themselves and the fetuses they carry. "Dr. Black told me that because of my tumor's size—about four inches—and its position," she says, "going into labor could be deadly for me and the baby, because of the pressure in my skull." Driscoll took steroids to ease the brain's swelling and hasten development of the baby's lungs. One month before her due date, she delivered a perfect baby, Declan, by C-section, and underwent neurosurgery five days later. Driscoll suffered no lasting effects from the 13-hour operation, and follow-up MR scans have shown no regrowth of her tumor.◆

Lisa Driscoll with sons Declan (right) and Taidhg, who was born last February at full term, without complications.