OncoLog
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Glioblastoma Cure Remains Elusive Despite Treatment Advances

By Bryan Tutt

Aggressive surgery followed by radiation therapy and chemotherapy offers hope of long-term survival for some patients with glioblastoma, but for most glioblastoma patients, the prognosis is poor.

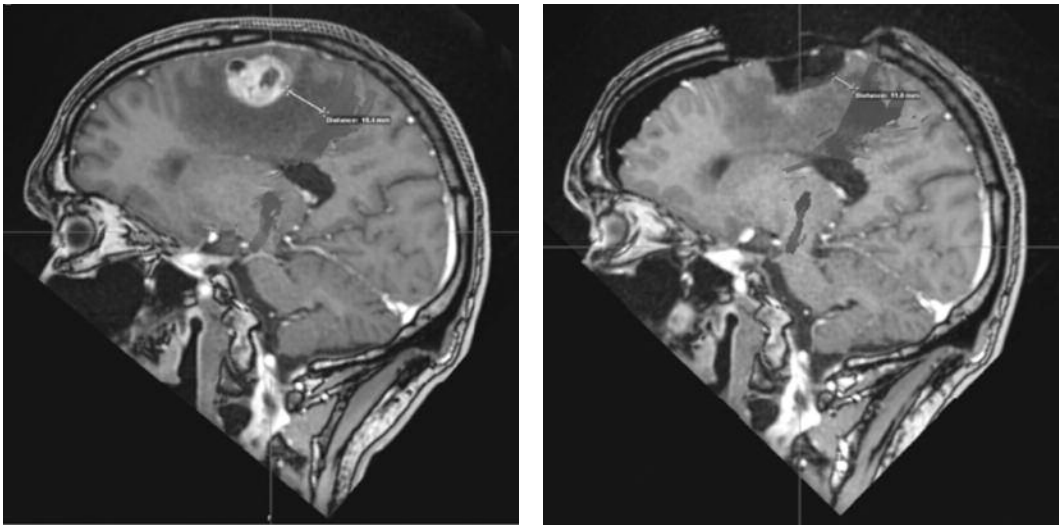
Twelve to fourteen thousand new cases of glioblastoma multiforme are diagnosed in the United States each year, and less than 10% of newly diagnosed glioblastoma patients survive 5 years. "Glioblastoma is a somewhat rare cancer, but it contributes to a large number of lost years of life because it hits people in their prime—their 30s, 40s, and 50s," said John de Groot, M.D., an associate professor in the Department of Neuro-Oncology at The University of Texas MD Anderson Cancer Center.

Brain tumors usually are detected by computed tomography or magnetic resonance imaging (MRI) after patients present with symptoms, but the final diagnosis of glioblastoma is not made until after the tumor is removed surgically and examined pathologically.

Surgery

Surgical resection, which requires a craniotomy, is almost always the first stage of treatment for patients with suspected glioblastomas. Because glioblastomas typically have cells that extend like thin tendrils several centimeters into the surrounding brain tissue, the entire tumor cannot be removed. However, surgery usually alleviates symptoms and can extend patients' survival.

"Most of the time, we recommend the most aggressive surgery possible," said Dr. de Groot. "If you can get out 92%–98% of the tumor, you can prolong patient survival." One of the most cited articles on this subject was published



Intraoperative MRI scans taken before (left) and after resection of a glioblastoma show the proximity of the motor fibers in the brain to the lesion.

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Glioblastoma Cure Remains Elusive Despite Treatment Advances

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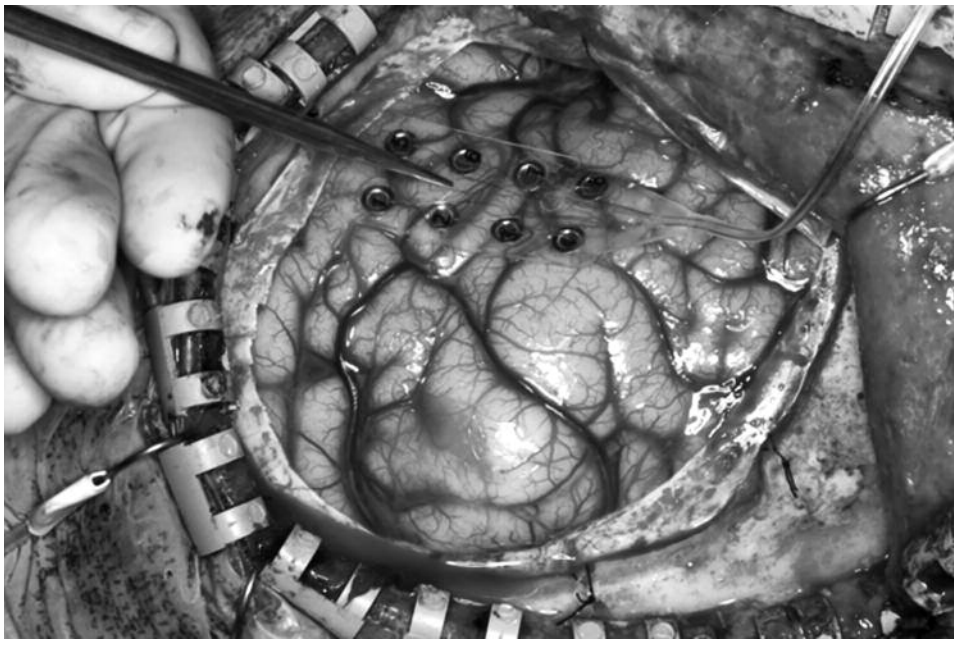
in the *Journal of Neurosurgery* by MD Anderson surgeons in 2001. This retrospective study of more than 400 patients with glioblastoma showed significantly longer survival times for patients in whom 98% or more of the tumor volume was resected than for those with a lesser extent of resection. More recent studies have corroborated those data. Although long-term survivors—those who live 5 years or longer after their diagnosis of glioblastoma—were rare in all studies, all such survivors had undergone very aggressive surgery.

During surgery for glioblastoma, it is standard practice to use stereotactic computer navigation. Before making their first incision, surgeons point an infrared sensor to anatomic landmarks on the patient to register the landmarks on a preoperative MRI scan loaded into a computer-based image guidance system. Surgeons can point the sensor at a structure during surgery to see the location of that structure on the image. "The navigation system helps us localize critical structures and navigate the patient's head. This allows us to be very precise with our incisions," said Ganesh Rao, M.D., an assistant professor in the Department of Neurosurgery who performs three or four glioblastoma resections in a typical week.

"The balance we're trying to strike is to remove as much tumor as we can without causing neurological damage," Dr. Rao said. In some cases, especially when tumors are located near the speech-generating centers of the brain, the best way to avoid neurological damage is to perform an awake craniotomy. During an awake craniotomy, a neuroanesthesiologist makes sure the patient is comfortable but still able to interact with the surgeons, who use an electrical probe to stimulate areas of the brain to determine which areas control certain functions.

Another tool used to help surgeons avoid inflicting neurological damage is preoperative functional MRI. The patient is asked to perform a task like saying a word or moving a hand, and the part of the brain responsible for that function will light up on the MRI scan.



During an awake craniotomy, surgeons use a grid electrode and direct electrical stimulation of the brain to identify and record the location of critical structures to be avoided during tumor resection.

"We can use that information and avoid those areas during surgery," Dr. Rao said.

MD Anderson surgeons have developed several tools to stimulate the brain and identify functions even when the patient is under general anesthesia. For example, surgeons can insert electrodes or needles into the major muscle groups of the arms or legs and use a probe during surgery to identify the areas of the brain being stimulated and register those areas in the computer navigation system. Surgeons can also stimulate a part of the brain during surgery to determine its function. "If I stimulate a certain part of the brain and the neurophysiologist tells me the arm is moving, I know this is a critical part of the brain that needs to be avoided during surgery," Dr. Rao said. "That's greatly increased the safety of these operations."

For a subset of patients, however, the stereotactic navigation system is not sufficient. Dr. Rao explained that many tumors take up the contrast dye used in MRI, which makes the difference between normal tissue and abnormal tissue very obvious on MRI and during surgery. But some brain tumors —especially low-grade tumors but also some glioblastomas—do not take up that dye. Although these tumors can still be distinguished from normal brain tissue, the difference in appearance can be subtle, both on MRI and in surgery.

Difficult-to-distinguish tumors are resected in MD Anderson's operative MRI suite, where MRI performed during the operation can help surgeons find and remove any residual tumor. Another benefit of the suite is that MRI can be performed to recalibrate the stereotactic navigation system during surgery. This recalibration is sometimes necessary because the effects of gravity or spinal fluid loss may cause the brain to shift during surgery, rendering the original image used for the stereotactic navigation system inaccurate.

The disadvantage of intraoperative MRI is the time it adds to the surgery. "A craniotomy for even the simplest tumor can take 2–3 hours," Dr. Rao said. "With intraoperative MRI, the average goes up to 6 or 7 hours, so we can do at most two operations a day in the MRI suite."

Following surgery, patients typically are up and walking within 24 hours and released from the hospital 2–3 days

later. However, some patients require a longer stay for rehabilitation, which may include speech therapy or physical therapy. "We've learned that the brain will recover from an insult," Dr. Rao said. "If we do our job as surgeons, these patients will recover; it just takes some time." Patients typically are able to begin chemotherapy and radiation therapy within a few weeks of surgery.

Chemotherapy and radiation therapy

Dr. de Groot said most glioblastoma patients will follow a standard treatment regimen after the tumor is resected. This consists of 6 weeks of external beam radiation 5 times a week plus oral temozolomide daily.

Anita Mahajan, M.D., a professor in the Department of Radiation Oncology, said the area around the original tumor is treated with photons (about 60 Gy) delivered in standard fractions using either three-dimensional conformal radiation therapy or intensity-modulated radiation therapy (IMRT). She said no difference in clinical results has been seen in the two systems, but IMRT is preferred because of the ease in planning. "IMRT gives us more flexibility to conform the dose to the target and to try to spare the other side of the brain, the brainstem, and the optic chiasm," Dr. Mahajan said.

After the 6 weeks of combined radiation therapy and chemotherapy, patients continue to receive temozolomide daily for 5 consecutive days in 28-day cycles for 1 year. This regimen was established by a 2005 study, conducted in Europe and Canada, in which patients given adjuvant treatment with temozolomide plus radiation therapy had more than double the 2-year overall survival rate of those treated with radiation only (27% and 10%, respectively). Even with this improvement, the 5-year overall survival rate for patients with glioblastoma remains low—around 8%.

"The treatment prolongs survival, but it's not destroying the microscopic extensions of the tumor," said Dr. de Groot. Unfortunately, most patients will have a recurrence of glioblastoma within 2 years of their original diagnosis. If a patient has a recurrence, a limited number of treatments are available.

"A second surgery is considered for patients with recurrent tumors when there's a question about the diagnosis or if it can be done very, very easily," Dr. Mahajan said. A second course of radiation therapy is sometimes given to patients whose cancer recurs in a different area of the brain. However, Dr. Mahajan said, 80% or more of glioblastoma recurrences occur in the same area as the original tumor, precluding additional radiation therapy because of toxicity concerns.

Chemotherapeutic agents may be used to treat recurrent glioblastoma. For example, bevacizumab was approved in May 2009 for the treatment of recurrent glioblastoma, and other

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CLINICAL TRIALS: Glioblastoma

The following clinical trials of treatments for glioblastoma are available at MD Anderson.

Randomized Phase II Trial of Standard-Dose Bevacizumab Versus Low-Dose Bevacizumab plus Lomustine in Adults with Recurrent Glioblastoma Multiforme (2009-0597). Principal investigator (PI): John de Groot, M.D. The goal of this clinical research study is to learn whether the combination of bevacizumab and lomustine can help to control glioblastoma.

Phase III Double-Blind Placebo-Controlled Trial of Conventional Concurrent Chemoradiation and Adjuvant Temozolomide plus Bevacizumab Versus Conventional Concurrent Chemoradiation and Adjuvant Temozolomide in Patients with Newly Diagnosed Glioblastoma (RTOG0825). PI: Mark Gilbert, M.D. The primary goal of this study is to find out if adding bevacizumab to the combination of temozolomide and radiation will help to control glioblastoma better than treatment with temozolomide and radiation alone.

A Phase I Dose-Finding Study of the Safety and Pharmacokinetics of XL184 Administered Orally in Combination with Temozolomide and Radiation Therapy in the First-Line Treatment of Subjects with Malignant Gliomas (2009-0476). PI: Dr. de Groot. The main goal of this study is to find the highest tolerable dose of XL184 that can be given in combination with temozolomide and radiation therapy to patients with anaplastic glioma or glioblastoma.

Phase I Trial of Conditionally Replication-Competent Adenovirus (Delta-24-RGD) for Recurrent Malignant Gliomas (ID01-310). PI: Frederick F. Lang, M.D. The primary goal of this study is to find the highest tolerable dose of Delta-24-RGD that can be injected directly into brain tumors and into the surrounding brain tissue where tumor cells can multiply.

Phase II Clinical Trial of ZYC300 in Recurrent Glioblastoma Multiforme Patients (2007-0673). PI: Amy Heimberger, M.D. The goal of this study is learn if the ZYC300 vaccine given in combination with two different dose schedules of temozolomide can help to control the disease in patients with glioblastoma.

A Phase II Open-Label Study of the Efficacy of TPI 287 in Patients with Glioblastoma Multiforme that Has Recurred or Progressed Following Prior Therapy with Radiation plus Temozolomide (2009-0759). PI: Charles Conrad, M.D. The goal of this clinical research study is to learn if TPI 287 can help to control glioblastoma. ■

FOR MORE INFORMATION

Visit www.clinicaltrials.org.

Assessing and Addressing the Biological Effects of Stress in Cancer Patients

By Joe Munch

Stress has long been linked to cancer progression. But the precise mechanisms by which stress exacts its pro-tumor effects are not fully understood.

At The University of Texas MD Anderson Cancer Center, researchers are working to better understand the role of stress in cancer patients to reduce its negative influence.

Chronic stress

"When people talk about stress, they are often actually talking about a stressor, meaning an event that is challenging, harmful, or that represents loss—an event that is overwhelming to the individual relative to the resources available to manage that situation," said Lorenzo Cohen, Ph.D., a professor in the Department of Behavioral Science and the director of the Integrative Medicine Program at MD Anderson. "But the event itself is not stress; a person's interpretation and then biological, psychological, and behavioral response to that event is stress."

According to Anil Sood, M.D., a professor in the Department of Gynecologic Oncology and the Department of Cancer Biology at MD Anderson, having some stress is not necessarily a bad thing. "Periodic episodes of stress are actually quite adaptive and can improve cognition, improve the ability to function, and enhance the immune system," he said.

When stress becomes chronic, however, it can have a negative overall effect on the body. Chronic stress—the kind of stress that can arise from being diagnosed with cancer or caring for a family member with a debilitating disease like Alzheimer's—is defined less by the type of stressor or its duration than by the individual's perception that the situation is perpetual and uncontrollable. "In chronic stress, there's basically no end in sight," Dr. Sood said.

The deleterious effects of chronic stress are many. "Regardless of the instigating event," Dr. Cohen said, "chronic stress creates a relatively uniform and profound biological effect on every system in the body, literally down to having an impact on how chromosomes function."

Stress and cancer

The research on stress and cancer is in its infancy. Stress has not been proven to initiate cancer; however, there is ample evidence suggesting that chronic stress can activate certain signaling pathways that can promote tumor growth, progression, and metastasis. But exactly which pathways are involved remains unknown. If the specific pathways can be identified—a feat complicated by the fact that cancer is not a single disease—they can be targeted with therapy to curb the effects of stress.

Most studies of stress in cancer patients have focused on the relationship between stress and the immune system. Instead of merely weakening the entire immune system, as was believed to be the case years ago, chronic stress actually dysregulates the immune system by suppressing the immunological processes that protect the body from viruses and malignancy (e.g., cellular immunity) and promoting the processes that make the body vulnerable to autoimmune disease and cancer progression (e.g., type II cytokine production).

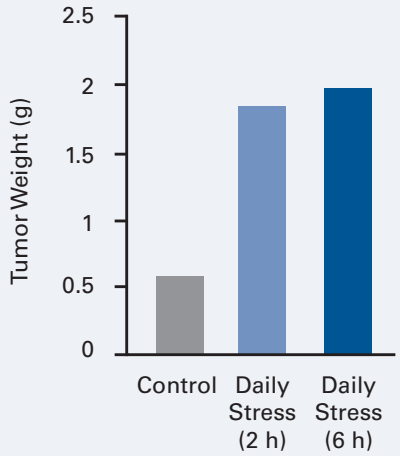
In other words, Dr. Sood said, "In a chronic stress setting, the balance of the immune system is shifted more toward helping the tumor grow."

Chronic stress elicits two major hormonal responses, each of which has distinct effects on the immune system that may facilitate cancer progression and metastasis. First, chronic stress overstimulates the hypothalamic-pituitary-adrenal axis, ultimately resulting in the prolonged release of glucocorticoids such as cortisol, which causes serious physiological changes in cardiovascular, metabolic, homeostatic, and immunological function. Second, the overstimulation of the hypothalamic-pituitary-adrenal axis spurs the ongoing release of the stress hormones epinephrine (adrenaline) and norepinephrine, which activate certain families of cell receptors, notably beta receptors. The downstream consequences of these receptors' activation include the activation of proinflammatory cytokine pathways that, in addition to creating inflammation, promote angiogenesis and suppress the body's immunological response to malignancy.

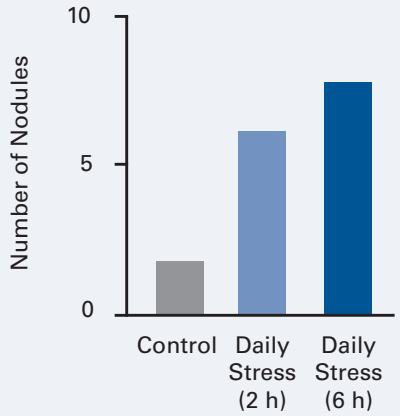
> **"In a chronic stress setting, the balance of the immune system is shifted more toward helping the tumor grow."**
>
> **– Dr. Anil Sood**

"There clearly seem to be effects of many of these stress hormones on the immune system. What these effects are and their magnitude and prevalence likely vary depending on the cancer type," Dr. Sood said.

Identifying the exact sources of these effects would allow researchers to target them with therapy. Given what is known today, future potential pharmacological interventions may include antiinflammatory agents such as naproxen and ibuprofen and beta-adrenergic blocking agents, or beta blockers, which are typically used to treat heart-related conditions such as angina and hypertension. According to Dr. Sood, the initial evidence supporting beta blockers, which inhibit many of the negative effects of stress in part by blocking the action of norepineph-



In a study of mice injected with human ovarian carcinoma cells, mice receiving 2 hours or 6 hours of stress daily for 21 days had significantly greater mean tumor weight and number of tumor nodules than mice not receiving stress. Source: Thaker PH, Han LY, Kamat AA, et al. Nat Med *2006;12(8):939–944.*



rine, is particularly tantalizing. For example, one large study several years ago found that among a number of patients on different antihypertension medications, the patients on beta blockers had the lowest incidence of prostate cancer. A more recent study found that breast cancer patients taking beta blockers were at lower risk of cancer progression and cancer-related death than breast cancer patients not receiving the drugs.

"Identifying those individuals who would be the most likely to be affected by stress pathways could very well be an achievable goal," Dr. Sood said. "For those patients, an individual intervention or cocktail of interventions could be optimal, but we are certainly not there at this point."

Stress management

The negative biological effects of chronic stress may also be countered by stress management techniques. Very little research has been done in this area. Dr. Cohen is working to elucidate the impact that behavior-based forms of stress management have on the biology of cancer and on clinical outcomes.

At MD Anderson's Integrative Medicine Center, patients are provided with resources to help manage their cancer-related stress, including conventional methods such as psychotherapy and cognitive behavioral therapy as well as traditional Eastern mind-body practices such as yoga, meditation, and tai chi. Research conducted at MD Anderson and elsewhere has shown that these types of mind-body practices affect stress hormones and other aspects of the immune system. "All these stress management techniques," Dr. Cohen said, "are offered on the basic premise of trying to dampen the sympathetic nervous system response, giving the person a chance to calm his or her mind, which in turn will help get the body back to equilibrium."

Such techniques, which can be implemented at any point of treatment, from early diagnosis through cancer survivorship, show promise in not only improving patients' quality of life but also tempering their bodies' biological responses to chronic stress. For example, Dr. Cohen and his colleagues found in one study that prostate cancer patients who were taught stress management skills had lower stress levels before undergoing radical prostatectomy and had better physical functioning 1 year after surgery than did prostate cancer patients who received supportive attention or standard care. They also found that the men in the stress management group had significantly higher immune function 48 hours after surgery than did the men in the supportive attention and standard care groups.

"We have a basic understanding that patients who are effectively able to manage stress in their lives are going to have better quality of life outcomes at minimum, and perhaps better clinical outcomes," Dr. Cohen said. "One question that remains is: What form of stress management is most effective? For example, is something like yoga—a quintessential mind-body practice made up of meditation, special breathing exercises, and special movements all put together in a systematic, cohesive approach—actually better than gentle stretching exercises and some simple relaxation techniques?"

A $4.5 million grant from the U.S. National Cancer Institute may help Dr. Cohen and his colleagues answer such questions. The grant, the largest awarded for the study of yoga and cancer, will enable the researchers to determine the benefit of incorporating yoga into treatment plans for breast cancer patients. Documenting the potential psychological and biological rewards of this and other types of programs in a rigorous scientific fashion is essential to changing the standard of care.

"Stress management needs to become much more a part of the standard of care," Dr. Cohen said. "It's not that all patients will be required to undergo stress management, but it needs to be something that is offered up front and that health care professionals encourage patients to participate in. And it needs to be made available across the cancer care continuum, from early diagnosis to long-term survivorship." ■

FOR MORE INFORMATION

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Dr. Anil Sood 713-745-5266
Integrative Medicine Center ...713-794-4700

ADDITIONAL RESOURCES

Cohen L, Parker PA, Vence L, et al. Presurgical stress management improves postoperative immune function in men with prostate cancer undergoing radical prostatectomy [published online ahead of print January 21, 2011]. *Psychosom Med.* doi: 10.1097/PSY.0b013e31820a1c26.

Moreno-Smith M, Lutgendorf SK, Sood AK. Impact of stress on cancer metastasis. *Future Oncol* 2010;6(12):1863–1881.

MD Anderson One of Four Centers to Test Cancer Cell Detection Chip

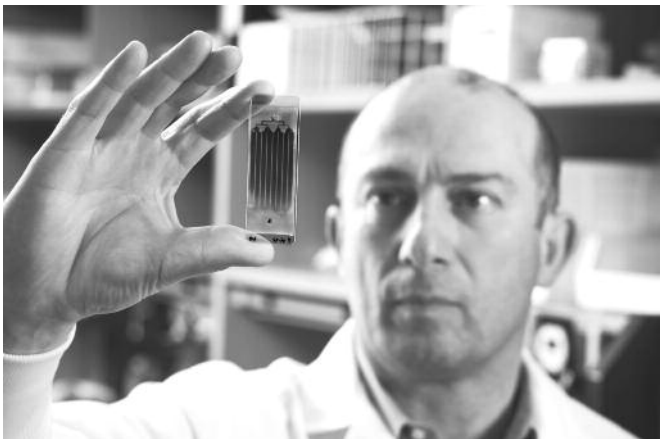
A new test that could monitor the effectiveness of cancer treatment by capturing circulating tumor cells from patients' blood samples, allowing the cells to be quantified and analyzed, is scheduled to begin clinical testing at MD Anderson and other institutions this year.

The test, which can detect 1 cancer cell among 1 billion healthy cells, is being developed at Massachusetts General Hospital in Boston.

An early version of the test used a microchip, called a CTC-Chip, which resembled a glass microscope slide with tiny posts that captured circulating tumor cells as blood was forced through the chip. The posts were coated with antibodies that would bind to tumor cells but not to normal blood cells. Stains then allowed researchers to count and capture the cells for analysis. The second-generation chip, called the HB-Chip, uses a herringbone design instead of posts to capture tumor cells and will be tested in clinical studies at MD Anderson and three other centers this year.

At MD Anderson, the HB-Chip will be used to capture circulating tumor cells in blood from patients in a number of settings, including the Biomarker-integrated Approaches to Targeted Therapy for Lung Cancer Elimination (BATTLE) II trial. Like the first BATTLE trial, whose results were reported in the June 2010 issue of *OncoLog*, BATTLE II will study four different chemotherapy regimens in patients with advanced, treatment-refractory lung cancer. Patient enrollment for BATTLE II is expected to begin soon.

"The number of circulating tumor cells could be a measure of the effectiveness of therapy," said Roy S. Herbst, M.D., Ph.D., chief of the Section of Thoracic Medical Oncology and a professor in the Department of Thoracic/Head and Neck Medical Oncology at MD Anderson. "In addition to quantifying the circulating tumor cells, our team wants to analyze these cells for genetic mutations, gene amplification, and expression of proteins—what many would call a liquid biopsy."



Dr. Mehmet Toner of Massachusetts General Hospital holds an HB-Chip, which captures circulating tumor cells from patients' blood samples. The chip is being tested in collaboration with MD Anderson and two other cancer centers.

For patients in the BATTLE II trial, blood samples will be drawn on the same day tumor specimens are obtained by core needle biopsy, before the patients begin treatment. The characteristics of the circulating tumor cells captured with the HB-Chip from the blood samples will be compared to those of the biopsy specimens; as part of the trial protocol, researchers will check both groups of tumor cells for biomarkers associated with effectiveness of therapy. The principal investigator of this trial is Vali Papadimitrakopoulou, M.D., a professor in the Department of Thoracic/Head and Neck Medical Oncology.

Researchers will also look at pharmacodynamic markers in circulating tumor cells obtained during and after treatment. Dr. Herbst said these analyses may help researchers better understand how cells respond to treatment and why some cells are resistant to therapy.

"The beauty of doing these tests at MD Anderson is that the large population of patients participating in clinical studies allows us to incorporate the blood tests into other clinical trial protocols," Dr. Herbst said. He added that it might be possible to test the HB-Chip in conjunction with upcoming clinical trials for the treatment of prostate, gastrointestinal, and breast cancers at MD Anderson.

The only blood test for circulating tumor cells currently on the market is CellSearch, made by Veridex, a Johnson & Johnson subsidiary. CellSearch detects circulating tumor cells but does not capture them intact. Because capturing the cells whole allows them to be analyzed like biopsy specimens, there is hope that the HB-Chip or one of its successors might also have predictive value or even eliminate the need for a needle biopsy in some patients in whom metastatic cancer is suspected. However, Dr. Herbst said he expects the main clinical use of the HB-Chip initially will be measuring a patient's response to therapy.

Several studies have found that circulating tumor cells are associated with poor prognosis in patients with various cancers, and it is believed that circulating tumor cells are an indicator of metastatic disease. However, the exact nature of the relationship between circulating cells and metastatic disease is not known. "Not all circulating tumor cells may have the ability to invade," Dr. Herbst said. "This is one of the things we hope to learn." ■

FOR MORE INFORMATION

Contact the Office of Physician Relations at 800-252-0502 or physicianrelations@mdanderson.org.

Yoga and Tai Chi

Two distinct disciplines offer similar physical and psychological benefits

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In the shadow of their New Year's resolutions, many people seek out the gym to improve their physical and mental well-being.

What a typical workout at the gym may lack, however, is a way to relax the mind, body, and spirit and a way to fight the stress inherent in our daily lives. Practicing yoga or tai chi can help calm the body's fight-or-flight response to stress.

Differences and similarities

Yoga, which originated in India, and tai chi, an ancient Chinese discipline, are distinct practices—but both seek to unite the mind, body, and spirit. Both practices have many styles, forms, and intensities.

By combining physical and mental disciplines, yoga can help you deeply relax and better manage the stress and anxiety in your life. Yoga has three main components: asana (physical postures and movements designed to increase your strength and flexibility), pranayama (breathing exercises), and meditation.

Together, these components are said to increase awareness and stimulate the free flow of prana (vital energy). Regularly practicing the yoga postures can prepare your body for meditation. The movement and controlled breathing help to quiet your mind and calm your muscles so that your mind can be clear to meditate.

People with limited flexibility may benefit from chair yoga—a gentle form of yoga practiced while sitting in a chair or standing and using a chair for support—or they may benefit from the continuous flowing movements of tai chi, which are typically performed while standing.

Tai chi, a system of martial arts that grew out of a Taoist pursuit of longevity, is typically practiced as a self-paced series of slow, flowing body movements that emphasize concentration, relaxation, and a conscious circulation of vital energy (chi) throughout the body. Despite its roots in martial arts, tai chi is usually practiced today as a way to reduce stress, calm the mind, and condition the body.

Benefits of mind-body exercise

Lorenzo Cohen, Ph.D., a professor in the Departments of General Oncology and Behavioral Science at The University of Texas MD Anderson Cancer Center, explained that yoga and tai chi share numerous physical benefits, including

- reduced heart rate and blood pressure
- increased cardiovascular efficiency
- increased flexibility and energy
- and improved posture and sleep patterns.

Tai chi has been found to reduce the risk of falls for elderly people. And some research has shown that yoga and tai chi can also bolster the immune system and decrease the production of stress hormones like cortisol, epinephrine, and norepinephrine.

The psychological benefits shared by yoga and tai chi include

- improved mood and feelings of well-being
- increased self-acceptance
- decreased anxiety and depression
- and improved concentration and memory.

Dr. Cohen said that chronic stress can literally get under our skin and into our cells. "Chronic stress causes our sympathetic nervous system to go into constant overdrive. With typical physical activity or exercise, a quieting of the mind does not happen. Practicing yoga or tai chi can dampen the sympathetic nervous system and calm the mind, thus helping to reduce your stress level."

When deciding what type of mind-body practice is best for you, Dr. Cohen suggests choosing whatever fits into your lifestyle. "Ask yourself which of these practices you will do on a daily basis," he said. "After 6–8 weeks of daily practice, you will begin to see physical improvements in your flexibility, your sleeping patterns, and your physical energy. It takes about 6 months of daily practice to see the inner transformation that brings about a pervasive calmness, self awareness, and an open heart." ■

– K.M. Speights

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Glioblastoma

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agents are available through clinical trials. "Although we go back to square one and think about all our options, the vast majority of our patients whose disease has progressed will be enrolled in a clinical trial," Dr. Mahajan said.

Ongoing research

New treatments for glioblastoma being developed and tested at MD Anderson include a conditionally replicative adenovirus that kills tumor cells without harming normal brain cells. And XL184, a small-molecule chemotherapeutic drug that inhibits multiple receptor tyrosine kinases, is being studied in several patient groups. Also being studied is a therapeutic vaccine designed to stimulate the immune system to elicit a cytotoxic T cell response against the tumor-associated antigen CYP1B1.

Studies in radiation therapy for glioblastoma focus mostly on treatment planning. "Currently, we plan our radiation therapy according to preoperative MRI scans," Dr. Mahajan explained. "Research is ongoing to determine whether other imaging modalities such as positron emission tomography, magnetic resonance spectroscopy, and a variety of high-end MRI techniques might better identify the areas at risk for tumor recurrence."

Research to improve the current treatment regimen for newly diagnosed glioblastoma patients is also ongoing. A phase III randomized study comparing two doses of temozolomide was recently completed at MD Anderson and other institutions. Those results will be published soon and are expected to further define the standard of care. "With more than 1,000 patients, it is certainly the largest study of glioblastoma that's ever been done. And it may turn out to be the most important such study because they've integrated tissue analysis to look for molecular markers, plus they are looking at measures of quality of life and neurocognitive outcomes," Dr. de Groot said.

A phase III study investigating the addition of bevacizumab to the standard adjuvant treatment regimen for newly diagnosed patients is underway at MD Anderson and other institutions. Although the results of this trial will not be known for several years, some physicians have begun prescribing bevacizumab off-label and adding it to the standard treatment regimen for newly diagnosed patients. Dr. de Groot said he did not recommend this practice because it is not yet known whether this experimental regimen is effective or alters long-term outcomes and because patients treated with bevacizumab would be ineligible for bevacizumab salvage therapy—or many clinical trials—in the event of a recurrence.

Until ongoing or future trials identify a better treatment, aggressive surgery followed by temozolomide plus radiation therapy and adjuvant temozolomide continues to offer glioblastoma patients the best hope of long-term survival. ■

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