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**On the cover:** Illustration of time-lapse microscopy of brain tumor cells migrating through the brain. Research under way in the Brain Tumor Center of Excellence is investigating how specialized enzymes allow glioma cells to maneuver through the small spaces between cells in brain white matter and cortex.
Dear Friends and Colleagues,

2011 was a memorable year for the Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center (BBTC), beginning in January when we officially changed our name in recognition of the Burkhardt family’s commitment to our mission.

The momentum continued throughout the year as we provided care for a record number of patients. We expanded the treatment options available to our patients with the addition of volumetric modulated arc therapy to our radiation oncology program and US Food and Drug Administration approval to begin using the new imaging agent 5-ALA to enhance tumor visualization during brain tumor surgery.

Through our robust translational research program we routinely offer our patients access to the newest experimental treatment options. In 2011, we treated patients with an experimental viral gene therapy as one of only three centers nationwide testing this promising new agent in clinical trials. An additional recognition of the BBTC as an important research center was the significant funding received by medical oncologist Manmeet Ahluwalia, MD, through Case Comprehensive Cancer Center. He will be Principal Investigator for a Phase II study of a new intravenous agent for treating brain tumors.

BBTC faculty continues to provide leadership locally and in the most prestigious professional societies in the country. Steven Rosenfeld, MD, PhD, was named Director of the Brain Tumor Center of Excellence in the Lerner Research Institute, and BBTC Associate Director Michael A. Vogelbaum, MD, PhD, was elected vice president of the Society of Neuro-Oncology in 2011.

To equip the future leaders of our profession to follow in the footsteps of our distinguished faculty, we continue to expand our fellowship offerings. In 2011 our first medical neuro-oncology fellow began an intensive year of training with us, bringing our total number of fellows to eight.

We closed out this remarkable year with a ceremony to celebrate our name change and honor Karen Wilson Smithbauer (daughter of Rose Ella Burkhardt) and her family for their generous support of our brain tumor program. It was a fitting end to a year of achievements.

I hope that you will share my pride in the BBTC’s accomplishments as you read this Year in Review publication.

Sincerely,

Gene H. Barnett, MD, MBA, FAANS, FACS
Director, Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center
Director, Cleveland Clinic Gamma Knife Center
Rose Ella Burkhardt Chair in Neurosurgery
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Director, Cleveland Clinic Gamma Knife Center
Rose Ella Burkhardt Chair in Neurosurgery
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Nancy Olivo
Research Accountant
Executive Summary

The BBTC continued its success in 2011, serving nearly 4,000 patients, with 40 percent of new patients coming from outside of Ohio. We expanded our services, improved patient satisfaction, made significant advances in translational research and offered a broad selection of educational experiences for clinicians and patients.

SOLID CLINICAL AND FINANCIAL PERFORMANCE

• 7,809 outpatient visits in 2011
• 994 surgical, Gamma Knife® and Novalis® procedures in 2011, including 121 Novalis radiosurgery cases
• Since 2001:
  – 95 percent increase in new patient visits,
  – 358 percent increase in total outpatient visits
  – 65 percent increase in total cases,
  – 12.6 percent increase in surgical cases
  – 130 percent increase in Gamma Knife cases.
• Largest market share in Ohio
• More than 40 percent of new brain tumor patients are from outside Ohio

STRONG RESEARCH FUNDING AND PHILANTHROPIC SUPPORT

• Research funding through three federal grants
• Nearly $4 million in philanthropic support since 2007 and more than $17 million since inception

PACESETTING CLINICAL PROGRAMS

• Advanced navigation using DTI and fMRI planning and intraoperative visualizations
• Growth in Novalis program from three cases in 2004 to 121 in 2011
• Leader in convection-enhanced delivery of advanced agents to brain tumors
• Second Gamma Knife Perfexion® unit in North America, performing 382 cases in 2011
• Leader in spinal radiosurgery with more than 500 procedures performed in 2011, more than 1,000 cases since program inception in 2004
• Integration of neuropsychology into clinical program

GROUNDBREAKING TRANSLATIONAL RESEARCH

• Charter member of National Cancer Institute-sponsored Adult Brain Tumor Consortium (ABTC)
• Leadership in national brain tumor organizations
• More than 40 active clinical trials
• Cutting-edge bench research in progress in more than a dozen laboratories

LOCAL, REGIONAL, NATIONAL AND INTERNATIONAL EDUCATION OUTREACH

• One of only three centers worldwide certified to teach introductory Gamma Knife to new practitioners, training more than 400 professionals to date

DISSEMINATING OUR KNOWLEDGE

• Publication of more than 100 journal articles, abstracts and book chapters in 2011
Overview

**INDIVIDUALIZED CARE BASED ON TRANSLATIONAL RESEARCH**

The BBTC has an international reputation for leadership in translational research that seamlessly and rapidly moves basic science discoveries from the laboratory to application in patient care. Our record of excellence in the diagnosis and treatment of primary and metastatic tumors of the brain, spine and nerves parallels our translational research program. As part of the Cleveland Clinic Neurological Institute, the BBTC collaborates with the Cleveland Clinic Taussig Cancer Institute to deliver the latest, most effective treatments to the patients who come here from around the world.

Through our team approach to patient care, the thousands of patients who entrust their care to us receive individualized treatment that combines therapeutic approaches from multiple specialties.

Our physicians and scientists participate in the most significant international research protocols. The BBTC has been a member of the prestigious New Approaches to Brain Tumor Therapy (NABTT) consortium, now the Adult Brain Tumor Consortium (ABTC), since 2000. Only institutions with the highest quality patient care and research programs qualify for membership. This National Cancer Institute-sponsored consortium is dedicated to improving outcomes for adults with primary brain tumors and sharing data from clinical and laboratory research that will guide further laboratory research on new treatments.

**CLINICAL PERFORMANCE – 2011**

Despite continued adverse economic conditions and unprecedented external pressures on healthcare, the BBTC in 2011 continued a positive trend in clinical volume. In 2011 BBTC physicians recorded 7,809 outpatient visits and performed 994 surgical, Gamma Knife and Novalis procedures.

**HIGHER PATIENT VOLUME**

Between 2001 and 2011, the BBTC experienced a 95 percent increase in new patient volume, a 358 percent increase in total outpatient visits, a 65 percent increase in total cases and a 130 percent increase in Gamma Knife procedures. Since BBTC physicians began performing Novalis radiosurgery in 2004, our patient volume for this procedure has grown, from three cases the first year to 121 in 2011.

**GROWTH IN MARKET SHARE**

The BBTC continues to maintain the highest market share for brain tumor diagnosis and care in the “Cuyahoga County,” “21-county” and “state of Ohio” markets and continues to increase dominance over its closest competitor. In 2011 BBTC physicians cared for about 4,000 patients. Beyond the local and regional markets, the BBTC is a national and international referral center, drawing new patients in 2011 from 25 states and seven countries.

BBTC physicians also work closely with neurosurgeons at Cleveland Clinic Florida to provide services for patients, bringing patients from Florida to Cleveland for care when needed.
Philanthropy

Generous supporters have contributed nearly $4 million to the BBTC since 2007 as gifts, pledges and estate bequests. Their support is essential to the innovative treatment, educational efforts and research that are the BBTC’s hallmarks. Our generous friends also contribute their time and invaluable service as members of the Neurological Institute and Taussig Cancer Institute Leadership Councils. In collaboration with physicians and the Cleveland Clinic development team, the Leadership Councils drive efforts to increase awareness and provide opportunities to support priority research and clinical initiatives.

PARTNERS IN NEURO-ONCOLOGY
The Burkhardt Brain Tumor Center extends deep appreciation to our Partners in Neuro-Oncology, each of whom has donated $1 million or more over their lifetimes in support of our programs.

Melvin H.* and Rose Ella* Burkhardt
Robert W.* and Kathryn* Lamborn

Alfred* and Norma Lerner
Mr. and Mrs. Lucius McKelvey
Ms. Karen Wilson Smithbauer

*deceased

The Burkhardt Brain Tumor Center is pleased to acknowledge the generous friends who support our mission financially.

Gifts of $25,000 or More
Central Distributors of Beer, Inc.
Mr. and Mrs. John R. Colina
Thomas Detesco, MD
Martin Drozdowicz, DDS
Mrs. Joyce D. Gagliarducci
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Mr. and Mrs. William R. Polkon
Mr. and Mrs. Eric Seres

Wolf Family Foundation
John C. York II, MD, and Ms. Denise DeBartolo York

Gifts of $1,000 or More
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Mrs. Inge Glasel
Ms. Steffi Gordinier
Mrs. Audrey Gornowicz
Green Synergy Enterprises
Ten years after surgery at the Burkhardt Brain Tumor Center (BBTC) to remove a malignant glioma, Lucius B. McKelvey is proud to say, “I’m in better health now than 15 years ago.”

The retired real estate executive, former CEO of Smythe Cramer Co., attributes his current state of health to the care he has received from the BBTC team, combined with the total makeover he has engineered in his own life.

In 2002 Mr. McKelvey had surgery at the BBTC to remove most of a tumor the size of a plum from deep in his brain. After surgery, Mr. McKelvey took a course of the medication temozolomide (Temodar) to minimize the growth of the remaining tumor matter. He continues to follow his Cleveland Clinic doctors’ orders to the letter with regular MRI scans and physical exams.

The experience was a wake-up call for Mr. McKelvey that brought his life into sharper focus and led him to make significant changes in his lifestyle to improve his overall health and bolster his immune system. “Not for one minute did I plan to die,” he says. “I put all my energy into a plan to live.” After recovering from the surgery, he sold his business to reduce his stress and focus on his family, adopted a vegetarian diet, started a regular exercise program and began sleeping eight hours a night.

Grateful for the dedication and expertise of Dr. Barnett and the entire BBTC team, Mr. McKelvey established The Sallie Turner McKelvey Endowment Fund, named for his mother, also a cancer survivor and now 91 years of age. Made in honor of Dr. Barnett, the gift has helped physicians in the Burkhardt Brain Tumor Center pioneer surgical procedures, develop imaging techniques and investigate possible treatments that ultimately will save lives.

Mr. McKelvey also provides generous support to The Scott Hamilton CARES Initiative to raise money for cancer research and education programs at Cleveland Clinic’s Taussig Cancer Institute. His particular interest is in research into the role of the immune system in fighting the growth of cancer cells.

Just as generous with his time as with his financial resources, Mr. McKelvey is a member of the Taussig Cancer Institute Leadership Council. His leadership has been instrumental in generating support for cancer and brain tumor programs and for building new partnerships. Mr. McKelvey shows his appreciation for the life-saving care he received at Cleveland Clinic by enjoying life to the fullest — spending time with his wife, Terrie, his grown children and grandchildren, enjoying his rediscovered woodworking hobby, exercising every day and tooling around the Chagrin Valley on his beloved Harley-Davidson. “This new life is wonderful!” he says.
Philanthropy

Grosse Ile Lawn Care & Maintenance Inc.
The Guidance Center
Hardwood Groves LTD
Ms. Barbara V. Heckman-O’Toole
Mr. and Mrs. Joseph D. Henderson
Mr. and Mrs. Todd A. Herzog
Mr. and Mrs. Robert R. Houston
Mr. and Mrs. Thomas E. Hutch Jr.
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Noel W. Jackson, DDS, and Sheri L. Snider, DDS
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World Heritage Foundation
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Mr. and Mrs. Robert J. Wright

* deceased
ENDOWED CHAIRS

The following endowed chair holders are entrusted with stewarding funds generated by gifts from generous benefactors to pursue research that advances the understanding and treatment of brain tumors.

Gene H. Barnett, MD, MBA, FAANS, FACS
   Director, Burkhardt Brain Tumor Center
   Director, Cleveland Clinic Gamma Knife Center
   The Rose Ella Burkhardt Chair in Neurosurgery

Candece Gladson, MD
   Endowed Chair in Neuro-Oncology Research

Tanya M. Tekautz, MD
   Co-Director, Pediatric and Adolescent Brain Tumor Program,
   Burkhardt Brain Tumor Center
   The Karen Colina Wilson Endowed Chair in Pediatric Brain Tumor Research

Michael A. Vogelbaum, MD, PhD
   Associate Director, Burkhardt Brain Tumor Center
   Director, Center for Translational Therapeutics
   The Robert W. and Kathryn B. Lamborn Chair for Neuro-Oncology

Robert J. Weil, MD, MBA
   Director, Laboratory Research, Burkhardt Brain Tumor Center
   Head, Pituitary and Neuro-Endocrine Surgery
   Director of Neurological Institute Surgical Operations
   The Melvin H. Burkhardt Chair in Neuro-Oncology Clinical Research
Every new treatment that improves patient care, quality of life or survival is built on a foundation of research discoveries. In the BBTC, we focus on translational research that creates two-way communication between laboratory researchers and physicians. Laboratory findings are translated into clinical trials of new treatments, and results from clinical trials inspire new investigations. Through this ongoing cycle, research discoveries are translated into new and better treatments for patients.
By continuing to attract leading laboratory and clinical researchers who advance our translational research efforts, the BBTC is striving to attain a National Cancer Institute (NCI) Specialized Program Of Research Excellence (SPORE) grant. SPOREs are a cornerstone of NCI’s efforts to promote collaborative, interdisciplinary translational cancer research. SPORE grants involve both laboratory and clinical/applied scientists and support projects that will result in new and diverse approaches to the prevention, early detection, diagnosis and treatment of human cancers.

Here, we highlight some of the most promising areas of our laboratory and clinical research programs and their application to patient care.

LABORATORY RESEARCH

Laboratory research expands our understanding of brain tumor development and growth and how we can interfere most effectively to disrupt those events. BBTC laboratory researchers are identifying the genetic, cellular and molecular biology of brain tumors; investigating the mechanism of tumor formation; and exploring new therapeutic developments for brain tumor treatments.

Center for Translational Therapeutics: Vogelbaum Laboratory

The Center for Translational Therapeutics, directed by Dr. Vogelbaum, performs pre-clinical testing of promising anti-cancer agents that may be useful in treating malignant brain tumors. The center’s goal is to move the drug testing process forward more quickly so that these new drugs may safely move into clinical trials sooner.

The center works with pharmaceutical companies and other medical institutions to test new compounds. The center’s efforts, including an international search for all potentially effective brain tumor therapies, have yielded several promising agents for testing. Several research projects are under way on drugs that work against malignant brain tumors based on the tumor’s molecular and genetic makeup.

Our researchers continue to explore alternative methods for drugs that overcome the body’s natural barriers that prevent drugs from entering the central nervous system. Dr. Vogelbaum’s ongoing research on convection-enhanced delivery (CED) offers a promising potential solution.

In CED chemotherapy drugs are delivered to the brain tumor via temporary catheters. This technique permits treatment with agents that would be too toxic to the body if delivered by IV or injection. The center is developing new drugs and devices for use with CED.

BRAIN TUMOR RESEARCH CENTER OF EXCELLENCE ESTABLISHED 2011

Cleveland Clinic Lerner College of Medicine of Case Western Reserve University established the Brain Tumor Research Center of Excellence in collaboration with Cleveland Clinic in 2011. The Center of Excellence is a collaborative “translational engine” in neuro-oncology dedicated to moving cutting-edge basic and translational research from Cleveland Clinic Lerner Research Institute into clinical care for BBTC patients.

This focus will lead to multi-institutional clinical trials of promising new agents, foster cooperation between researchers and the biotechnology and pharmaceutical industries and support applications for multi-investigator grant awards. Ultimately, the Brain Tumor Research Center of Excellence will seek a grant as a brain tumor Specialized Programs of Research Excellence (SPORE) through the National Cancer Institute Translational Research Program.

The BBTC participated in the recruitment of Steven Rosenfeld, MD, PhD, as director of the Research Center of Excellence. Dr. Rosenfeld brings extensive and impressive experience in brain tumor research to the position, including 10 years as director of the University of Alabama brain tumor research and treatment program.

Dr. Rosenfeld is a graduate of Harvard University. He earned a PhD in biophysics from the University of Chicago and his medical degree from Northwestern University School of Medicine. He joined the BBTC from the Neurological Institute at Columbia University, New York, NY, where he has been the John and Elizabeth Harris Professor and chief of the Division of Neuro-Oncology since 2005.
Researchers in Dr. Vogelbaum's laboratory also are collaborating with the Lerner Research Institute Department of Biomedical Engineering on nanotechnology, the manipulation of structures at the molecular level, another sophisticated new technique that may enhance drug delivery to the brain.

The center's first translational clinical trial, a Phase II trial of erlotinib (Tarceva®), showed encouraging results. It also raised important questions about the drug’s ability to penetrate into the brain. As a result, the center launched a follow-up trial in which patients undergo a tumor biopsy while receiving drug therapy to determine whether the drug’s effects depend on its ability to reach the intended tumor target.

The center also works closely with other laboratories at Cleveland Clinic that are developing novel therapeutics that may have applications for malignant brain tumors. The center has evaluated methods for improving the immune response to gliomas and expanded the understanding of the immune response in regulating glioma cell migration. Center researchers continue to explore a new drug that may make brain tumors sensitive to the drug temozolomide and continue investigating the role of a specific gene in formation of new blood vessels in tumors.

**Gladson Laboratory**

Dr. Gladson’s laboratory is investigating novel anti-angiogenic agents, substances that interfere with new blood vessel formation. These agents can be used to block the growth of new blood vessels in malignant glioma tumors, such as glioblastoma, and metastatic tumors to the brain. Her research is a collaborative effort among the Department of Stem Cell Biology and Regenerative Medicine, Abbott Laboratory and the BBTC.

In a recent study, Dr. Gladson’s team demonstrated that an anti-tumor response occurs in the brain of brain tumor patients who have a longer survival. The researchers determined that the cells lining tumor blood vessels contain two substances that inhibit new blood vessel formation, tumor necrosis factor receptor 1-TNFR1 and tumor necrosis factor α-TNF. They also discovered molecules in the brain that regulate the production of TNF — two that increase the production and one that inhibits it. They are now testing whether activating the TNFR1 death receptor in blood vessel lining cells is a potential way to inhibit new blood vessel formation in brain tumors.

**THE ROSENFELD LABORATORY**

Investigators led by Steven Rosenfeld, MD, PhD, are studying the role of molecular motors — a family of enzymes that move cells or parts of cells — that enable glioma cells to grow and invade through the brain white matter and cortex. They have shown that four specific molecular motors are essential to this process, making them potential targets for new agents that could block tumor invasion and growth. The work on these molecular motors is organized around three projects.

In the first project, Dr. Rosenfeld is examining how two of these motors, myosins IIA and IIB, allow glioma cells to maneuver through the small spaces between cells in brain white matter and cortex. This work involves a time-lapse record of tumor cell migration in the brain taken through a microscope and studies of brain tumor cell migration and growth using synthetic substrates with defined mechanical properties. Hand-in-hand with these studies are experiments in rodent models examining the effectiveness of new agents that target these myosins.

In the second project, investigators are examining how myosin VI and its binding partners are used by glioma cells to respond to growth — and invasion — promoting signaling molecules that are found within the brain tumor microenvironment. They have shown that inhibiting myosin VI reduces the effects of these growth factors.

The third project involves examining the role of a different class of molecular motors, the mitotic kinesins, in glioma growth and invasion. These motors play a central role in cell division. The Rosenfeld laboratory also has shown that they appear to be important in driving glioma invasion as well. Pharmacologic inhibitors of these motors are available, and the Rosenfeld laboratory is exploring the efficacy of these drugs in animal models of glioma.
Brady-Kalnay Laboratory

Susan Brady-Kalnay, PhD, and her team are investigating the role of a novel enzyme in regulating the invasion and migration of malignant glioma cells. In collaboration with Dr. Vogelbaum, this project obtained $1.9 million in NIH funding that extended through 2011.

Gerson-Liu Laboratory

Stanton Gerson, MD, and Lili Liu, PhD, are recognized authorities on the role of DNA repair enzymes in tumor cell resistance to chemotherapy. In collaboration with Dr. Vogelbaum, they are evaluating the roles of certain biologic pathways in this process.

Rich Laboratory

Although brain tumors continue to challenge medical science in many ways, the understanding of how these tumors behave in such deadly fashion is advancing rapidly. Cleveland Clinic is now home to the greatest number of research groups in the United States dedicated to new models of brain tumors.

BBTC researchers have found that brain cancers contain cells called brain tumor stem cells that are resistant to current cancer treatments. Jeremy Rich, MD, chair of the Department of Stem Cell Biology and Regenerative Medicine, is a clinical neurologist and a world-renowned expert on brain tumor stem cells. His laboratory focuses on the potential role of these cells in brain tumor development and treatment.

Researchers in the Rich laboratory continue to make significant progress on devising new ways of killing these cells, approaches that have the potential to translate to better treatments for brain cancer. They have teamed with clinical researchers to evaluate new drugs for brain tumors that sensitize brain cancer stem cells to radiation. Other studies have found that cancer stem cells have a protective mechanism, directed by the A20 gene, that allows them to deal with stress and inflammation. Blocking this A20 gene kills cancer stem cells and sensitizes them to other drugs.

These are only a few examples of the multiple unconventional approaches to treatment that the Rich laboratory is pursuing. Dr. Rich and his team believe that developing treatments that target cancer stem cells will ultimately give patients hope for longer and better lives.

Dr. Rich’s team also is investigating the effects of glioma on the immune system, the body’s natural defense mechanism. Prior studies of malignant gliomas have shown that these tumors suppress the immune system’s normal activity. Investigators suggest that stimulating the immune system in combination with agents that reduce this immune suppression effect may be a potent therapy for brain tumors.

To this end, the Rich laboratory has been working to advance the understanding of the biologic pathway that leads to immunosuppression. The team has identified a potential mechanism for how the damage to the immune system occurs and a protein that appears to be critical to the process. They are studying T-cells (the main cells in the immune system) from brain tumor patients to determine if they are different from T-cells in healthy people.

Center for Cerebrovascular Research

Under the direction of Damir Janigro, PhD, the center is investigating protein markers for brain metastases in patients with lung cancer. The center collaborates with the departments of Pulmonary Medicine and Hematology/Oncology and the Section of Neuroradiology on this research.

In a recent study, center researchers determined that 65 percent of patients with lung cancer seen at Cleveland Clinic over a five-year period had small vessel ischemic disease (SVID) by magnetic resonance imaging (MRI). Patients with SVID appeared to have a lower incidence of brain metastases compared with those who did not have SVID. The center also studied serum from lung cancer patients with SVID with or without brain metastases. Researchers were able to identify a specific protein that was not elevated in the patients with SVID as a marker for brain metastases.

BBTC surgeons remove tumors from the brain using image-guided techniques that enhance the safety and precision of the procedure.
CLINICAL RESEARCH

Developing new and innovative treatments for patients with benign and malignant brain tumors is an important element of our mission. As part of this process, many of our patients have the opportunity to participate in clinical trials that evaluate experimental drugs or devices. In 2011, 56 patients enrolled in treatment trials and 254 donated blood or tissue for studies. Current clinical trials are testing agents that stimulate the immune system and agents that interfere with blood vessel development and tumor stem cell growth. New devices for drug delivery and laser ablation are also being studied.

The BBTC has been a member of the prestigious Adult Brain Tumor Consortium (ABTC) since its formation in 2009 and was a member of ABTC’s predecessor organization, the NABTT, since 2004. The ABTC, the only consortium funded by the National Cancer Institute to conduct Phase I and II trials of new treatments for brain tumors, includes 18 Centers of Excellence for brain tumor research. BBTC physicians have served as national principal investigators on two clinical trials sponsored by the ABTC, and the BBTC ranks second among ABTC members in number of patients enrolled in clinical trials.

The BBTC also participates in other prominent cooperative research groups:

- Radiation Therapy Oncology Group (RTOG)
  - Dr. Vogelbaum is co-chair of the Brain Tumor Committee and chair of the Neurosurgery Committee
- Children’s Oncology Group (COG)
- North American Gamma Knife Consortium (NAGKC)

BBTC physicians play leadership roles in numerous multicenter trials that have the potential to change the course of brain tumor treatment. Some of the clinical trials they are leading include:

- ABTC 0906: A Phase II and Pharmacodynamics Trial of RO4929097 for Patients with Recurrent/Progressive Glioblastoma (Dr. Peereboom, Study Chair)
- RTOG 0825: A 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 (Dr. Vogelbaum, Neurosurgery Study Chair)
- RTOG 0834: Phase III Trial on Concurrent and Adjuvant Temozolomide Chemotherapy in Non-1p/19q Deleted Anaplastic Glioma. The CATNON Intergroup Trial. (Dr. Vogelbaum, U.S. Principal Investigator)
- RTOG 0539: Phase II Trial of Observation for Low-Risk Meningiomas and of Radiotherapy for Intermediate- and High-Risk Meningiomas (Dr. Vogelbaum, Neurosurgery Co-Chair)

Additional clinical research projects include these Cleveland Clinic investigator-initiated studies:

A Prospective First-in-man (FIM) Safety Trial of the AutoLITT Laser Treatment of Recurrent/Progressive Brain Tumors (Dr. Barnett, Study Chair)
  - Dr. Barnett was the first to use this device to directly apply ablative laser therapy to the tumor.

A Phase I/II Trial of SRS Plus Bevacizumab in patients with recurrent/progressive GBM (Dr. Vogelbaum, Study Chair)

Phase II Trial of Sunitinib Delivered as Maintenance Therapy After Stereotactic Radiosurgery In Patients with 1-3 Newly Diagnosed Brain Metastases (SUNDANCE Trial) (Dr. Peereboom, Study Chair)

BBTC TESTS GENE THERAPY FOR GBM

The BBTC is one of the first three centers in the United States to participate in a first-in-human Phase I/II trial of Toca 511, a retroviral gene therapy developed by the San Diego-based biopharmaceutical company Tocagen. Michael A. Vogelbaum, MD, PhD, is the Principal Investigator of this trial at Cleveland Clinic.

The trial is testing the new agent in patients with advanced glioblastoma (GBM) that has recurred after surgery, radiation and chemotherapy. Patients receive a single dose of Toca 511 delivered directly to the tumor followed by an oral chemotherapy drug given monthly for six consecutive days. The BBTC is also testing the use of Toca 511 gene therapy in patients who have undergone surgical removal of a recurrent GBM. In these patients, the virus is injected into the area where the tumor was removed.

At the time of this report, the BBTC has enrolled patients in the biopsy-injection trial, and one patient in the surgical removal-injection trial. Data analysis is in progress, and preliminary results will be announced soon.
Intraoperative radiation therapy for solitary brain metastases (Dr. Weil, Study Chair)

- Dr. Weil is conducting this Phase I/II study utilizing INTRABEAM®, a novel delivery system for radiation therapy that allows the precise delivery of radiation directly into the tumor cavity and allows the patient to postpone the need for whole brain radiation.

Clinical Study to Assess Entry of Chemotherapeutic Agents into Brain Metastases in Women with Breast Cancer (Dr. Weil, Study Chair)

- Dr. Weil is Cleveland Clinic’s Principal Investigator on a Department of Defense Center of Excellence grant for the eradication of breast cancer brain metastasis.
- Dr. Weil and Dr. Peereboom are leading a study in which a breast cancer chemotherapy drug is given prior to surgical removal of a breast cancer brain metastasis. The tumor sample is assayed for drug concentration to assess the drug’s entry into the metastatic tumor.

Studies for which Cleveland Clinic BBTC physicians serve as co-investigators include:

A Phase I Dose-Escalation Study of XL765 in combination with Temozolomide in Subject with malignant gliomas (Dr. Ahluwalia, local Principal Investigator)

A Phase 2 Non-Comparative Randomized Open-Label Study of Multiple Regimens of Single-Agent XL184 in Subjects with Grade IV Astrocytic Tumors in First or Second Relapse (Dr. Ahluwalia, local Principal Investigator)

A Prospective, Multi-center Trial of NovoTTF-100A Together With Temozolomide Compared to Temozolomide Alone in Patients with Newly Diagnosed GBM (Dr. Barnett, local Principal Investigator)

A Phase 1 Ascending Dose Trial of the Safety and Tolerability of Toca 511 in Patients with Recurrent Glioblastoma Multiforme (Dr. Vogelbaum, local Principal Investigator)
Clinical Care

A focus on developing practical clinical applications based on findings from translational research is the hallmark of our multidisciplinary team approach to patient care. Our physicians and surgeons work together to create an individualized treatment plan for each patient that combines the latest investigational treatments, molecular and chromosomal testing and proven therapies. Because brain tumors are extremely complex lesions that often require several different types of therapy, the BBTC offers the full range of treatment options to ensure that our patients receive the best possible care.

Dr. Barnett and radiation oncologist John Suh, MD, review a patient’s series of MRI scans to evaluate tumor status following radiation therapy.
MEDICAL NEURO-ONCOLOGY

Medical neuro-oncology includes chemotherapy and biologic therapy. In this rapidly changing field, many new treatments are being developed that may improve quality of life and extend survival. Our medical neuro-oncologists are experts in the use of established anti-tumor drugs and leaders in the testing of new agents that target specific tumor molecules. These agents are a new type of chemotherapy that reduce the rate of cell growth but do not kill the tumor directly.

Our medical and surgical neuro-oncology team attends daily clinics and twice-weekly brain tumor boards to discuss each patient's treatment plan and progress. Through these discussions, the team agrees on the individualized plan for each patient that includes the best mix of medical, surgical and radiotherapy treatment. The team also takes care of our patients in the long term to manage anti-seizure medications if needed and monitor the neurocognitive impact of the tumor.

NEUROSURGERY

BBTC neurosurgeons have made surgical treatment possible for more brain tumors through their use of laser surgery, skull base techniques, microsurgery, endoscopic surgery, intraoperative magnetic resonance imaging (iMRI), radiation implants, radiosurgery and sophisticated computer-assisted techniques. Surgical navigation systems developed by Cleveland Clinic's Center for Computer-Assisted Neurosurgery have reduced wound and neurologic morbidity, operating time, costs and length of stay for many brain tumor surgeries. The latest imaging technology such as diffusion tensor imaging (DTI) fiber tracking and functional MRI (fMRI) allows the surgeon to see critical brain pathways and surface areas, making brain tumor surgery safer.

The BBTC has been developing and using intraoperative MRI (iMRI) since the late 1990s. This imaging technology provides critical navigational guidance and monitoring for tumor resection (surgical removal). Since 2010, BBTC surgeons have been performing neurosurgery in a dedicated high-field iMRI suite. The state-of-the-art imaging technology in this suite delivers high-quality images throughout the procedure so the surgical team has continual guidance for even the most intricate tumor resection. The suite is also used for other neurosurgical procedures such as placement of stereotactic EEG electrodes, cranial biopsies and laser ablation therapy for intracranial neoplasms.

BBTC neurosurgeons use minimal-access techniques to resect brain metastases that can be surgically removed. These small-incision techniques allow patients to go home sooner and recover faster, with less pain.

Surgical removal of the metastases plus whole-brain radiation therapy is more effective in treating brain metastases than radiation alone, but whole-brain radiation can have significant side effects. BBTC clinical researchers are investigating the use of chemotherapy during surgery or radiosurgery after resection as alternatives to whole-brain radiation. Surgery may be part of a comprehensive plan that includes other techniques to treat additional brain metastases such as radiosurgery or systemic chemotherapy.

Convection-Enhanced Delivery (CED)

The BBTC is a leader in the clinical development of CED. Early trials have shown CED to be effective, but Phase III clinical trials have not been positive. The BBTC is participating in the development of new types of catheters and drugs to maximize CED's effectiveness. BBTC physicians also are involved in clinical trials related to CED, and the BBTC has hosted the only international symposia focused on this treatment.

In addition to his work on CED in the Center for Translational Therapeutics, Dr. Vogelbaum is collaborating with Cleveland Clinic Innovations on a new type of CED catheter for use in clinical trials. Dr. Vogelbaum is Founding President of the Society for CNS (central nervous system) Interstitial Delivery of Therapeutics, the first international organization dedicated to research in this technique.
Laser Interstitial Thermal Therapy
The BBTC has been using the AutoLITT (laser interstitial thermal therapy) since 2008. We were first in the world to use this laser-based system in humans for minimally invasive treatment of a brain tumor. The system uses a special, high-precision laser probe to coagulate tumors with the heating monitored by MRI.

Dr. Barnett led the first clinical trial of this system in humans in collaboration with University Hospitals Case Medical Center and the Case Comprehensive Cancer Center. Preliminary results suggest that this technology could offer the benefits of conventional surgery to some patients with inoperable tumors or spare patients more invasive treatments. Based on these results, the FDA approved the AutoLITT system in 2009.

The BBTC was one of the first centers in the world to implement the AutoLITT in clinical use. Integrating the AutoLITT into the center’s IMRIS intra-operative imaging system has enhanced patient safety and reduced total imaging and treatment time.

RADIATION NEURO-ONCOLOGY
Radiation neuro-oncology is the use of high-energy rays to damage or destroy cancer cells. Cleveland Clinic has long been a leader in developing and applying new technology in radiation oncology, dating back to 1989 when Ohio’s first noninvasive ablative cancer treatment was performed here.

Today, the BBTC offers Gamma Knife, intensity-modulated radiotherapy (IMRT), intraoperative radiation therapy (IORT), brachytherapy and image-guided radiation therapy (IGRT). These technologies may control lethal tumors for longer periods than conventional radiation therapy, decrease the potential side effects of radiation therapy and benefit patients who may not be healthy enough to undergo a lengthy microsurgical procedure.

Shrinking-Field Radiation Therapy
Tumor cells often can be found centimeters away from the primary tumor mass, but surgically removing the main tumor does not remove tumor cells that have spread beyond it. As many as 80 to 90 percent of tumor recurrences occur within 2 cm of the site of tumor removal. The shrinking-field

Laser interstitial thermal therapy using the AutoLITT uses MRI to guide placement of a laser probe directly at the tumor’s location. The laser heats and burns out the tumor while cooling surrounding areas to prevent damage to normal brain tissue.

Dr. Gene Barnett was Principal Investigator on the first clinical study to use the AutoLITT in humans, and the BBTC was among the first in the world to introduce this technology for clinical use.
technique of radiation therapy was developed to kill these tumor cells by delivering the highest radiation dose to the area around the site where the brain tumor was removed.

We continue to pursue advances in other therapies to treat the edges of the tumor removal area, as well as areas of the brain that contain tumor cells that are distant from the original tumor site.

**Radiosurgery**

The BBTC has one of the most robust radiosurgery programs in the country, offering Gamma Knife, Novalis, spinal radiosurgery and cranial radiosurgery.

**Gamma Knife**

We have been performing radiosurgery with the Gamma Knife since 1997, treating nearly 4,000 patients with this technology by the close of 2011.

Gamma Knife Perfexion radiosurgery, the most advanced form of Gamma Knife, focuses the energy beams very tightly so that aggressive high-dose radiation can be directed at the tumor — even those deep in the brain — without harming surrounding normal brain tissue. Gamma Knife is ideal for small tumors and requires only a single one- to two-hour treatment. In 2011, we performed 382 Gamma Knife Perfexion radiosurgery cases.

The BBTC Gamma Knife Center is one of only three centers worldwide certified by Elekta (the sole manufacturer of the Gamma Knife) to train physicians and medical physicists new to Gamma Knife radiosurgery.

**Novalis**

Novalis is an image-guided system for radiosurgery and fractionated conformal radiosurgery, the delivery of repeated low doses of radiation to the brain and tumor. This technology allows the safe treatment of lesions that are near critical structures such as the optic nerve and re-treatment for some patients who have had conventional radiotherapy.

At Cleveland Clinic, Novalis is used for larger malignant or benign tumors. We also use this technology for treating tumors outside the brain, particularly primary and metastatic spinal tumors that are difficult to treat because they are close to critical structures. Since 2007, the BBTC has been one of the busiest spine radiosurgery programs in the nation using the Novalis platform, treating more than 500 cases to date.
SECTION OF METASTATIC DISEASE SURGERY

The BBTC has one of the most robust programs in the country treating metastatic tumors in the brain, offering minimally invasive neurosurgery and spinal and cranial radiosurgery with the Gamma Knife and Novalis.

**Cranial Radiosurgery (Gamma Knife and Novalis)**

Gamma Knife is very effective in treating brain metastases, and these are the most common type of tumor we treat with this technology. Gamma Knife can be used to treat metastatic tumors that cannot be reached by conventional surgical techniques, and the results are comparable to surgery plus radiation therapy.

So-called “radio-resistant” tumor types (tumors that do not respond to conventional radiotherapy) do respond to Gamma Knife. When Gamma Knife is used in accord with guidelines set by the Radiation Therapy Oncology Group (RTOG), neurologic and cognitive side effects are minimal.

Novalis is indicated for patients with metastatic brain tumors that are not ideal for Gamma Knife radiosurgery. Novalis also can be used for metastases outside the brain such as metastatic spinal tumors and prostate and lung cancers. The Department of Radiation Oncology has been designated a “Center of Excellence” in the use of Novalis.

The Elekta Synergy™-S unit offers another option for treating brain metastases.

**Spinal Radiosurgery**

Between 60 and 85 percent of cancer patients experience bone pain caused by metastatic tumors. When the metastases involve the spine, disabling pain and destruction of the individual vertebra can occur, leading to spinal instability, spinal cord or nerve root compression and, ultimately, neurological problems and paralysis. Early detection and intervention are essential to minimize these consequences.

*Lilyana Angelov, MD, and Samuel Chao, MD, plan a patient’s radiosurgery to treat metastatic tumors.*
Cleveland Clinic established the Stereotactic Spine Radiosurgery (SRS) program in 2006, the first spine radiosurgery program in Ohio. One of the premier programs in the country, the SRS offers outpatient spine radiosurgery to treat metastatic tumors in the spine using Novalis technology. Patients experience rapid, effective pain and tumor control with minimal risk of side effects.

Stereotactic spinal radiosurgery has revolutionized the treatment of malignant primary and metastatic spine tumors and many benign tumors. Our experience with radiosurgery alone and in combination with other therapies demonstrates that this treatment is an effective option for patients with spine lesions. In the more than 500 patients with spine tumors treated here, we have achieved clinically significant pain relief in more than 85 percent and local tumor control in 90 percent of patients with a single outpatient, noninvasive treatment.

Other options available here for the treatment of spine tumors include open surgical procedures, minimally invasive surgery, vertebral augmentation, conventional chemotherapy and radiation therapy, surgical pain management interventions, palliative care and a variety of clinical trials.

Chemotherapy
Most commonly used chemotherapy agents have difficulty getting through the body’s natural barrier that protects the brain's circulation system. This means that many types of cancer take refuge in the brain, where chemotherapy cannot reach them. Treatment options that can attack these tumors hiding in the brain include hormone therapies; capecitabine; methotrexate; lapatinib; patupilone, which belongs to a new class of cytotoxic drugs; and temozolomide, a newer oral agent.

As our understanding of tumors at the molecular level expands, investigational drugs that target specific biologic pathways in a tumor may play an increasing role in the management of brain metastases. This is an exciting area of translational research in the BBTC.

SPECIALIZED CLINICAL PROGRAMS

Pediatric and Young Adult Brain Tumor Program
This program serves children with cancers that affect the developing brain and spinal cord. Cleveland Clinic’s dedicated pediatric neurosurgery and neuro-oncology teams use the latest diagnostic and treatment approaches to provide pediatric and adolescent patients the most advanced care available and maximize their quality of life. Since 2004, our pediatric patient volume has grown more than 42 percent from 413 to nearly 600 outpatient visits in 2011.

The team creates an individualized treatment plan for each child that includes specialized inpatient and outpatient care. A multidisciplinary brain tumor board meets twice a week to review cases and plan the most effective treatment for each patient.

The BBTC conducts a multidisciplinary clinic for children and adolescents with brain tumors twice a week. Each child’s care team includes a physician, a nurse practitioner and a registered nurse. A pediatric anesthesiologist is available for sedation to reduce the anxiety of neuro-imaging for our young patients. Neurosurgeons and radiation oncologists are available as needed. The nurses contact the patient’s family at home on a regular basis to monitor pain management and other medical issues.

Cleveland Clinic Children’s Hospital offers a full range of therapeutic services for in- and outpatient rehabilitation. Children and adolescents who have been treated for a brain tumor can benefit from programs and services that support normal physical and cognitive development and functional improvement and prevent disease complications.

Von Hippel Lindau Virtual Clinic
Von Hippel Lindau syndrome is a rare genetic disease characterized by tumors in the central nervous system, adrenal glands, kidneys and pancreas. The BBTC has participated in the multidisciplinary von Hippel Lindau virtual clinic since 2005, helping to coordinate comprehensive care for patients with this condition.

Specialists in genetics, neuro-oncology, urology, gastroenterology, hematology/oncology, ophthalmology and endocrine surgery provide patient education, surveillance and disease management to maximize quality of life for these patients.
Clinical Care

Center for Neurofibromatosis and Benign Tumors

The Center for Neurofibromatosis and Benign Tumors has provided multidisciplinary care to children and adults with neurofibromatosis (NF) for three decades. Physicians in the center are nationally recognized experts in the diagnosis and treatment of all forms of NF. They have participated in and developed clinical trials of new drugs for the brain tumors and plexiform neurofibromas that affect the lives of many NF patients.

A team of neurologists evaluates each patient, determines which other specialty physicians and services at Cleveland Clinic are necessary and coordinates care. Because of our large patient volume, Cleveland Clinic specialists in many disciplines have extensive experience in treating NF complications. Surgeons in the Section of Skull Base Surgery focus on management of the benign brain tumors often found in NF, including meningiomas and schwannomas. Surgeons in the BBTC and Spine Center have extensive experience in the surgical removal and spinal stabilization procedures often required in NF.

Spinal radiosurgery techniques offer a noninvasive method for treating some tumors.

Section of Skull Base Surgery

The skull base is the sloped, bony area behind the eyes and nasal cavities that creates the floor of the skull. Many tumors originate in or extend into the skull base. Even non-cancerous skull base tumors can cause many problems that affect the patient’s quality of life.

Treating skull base tumors presents some challenges because they are close to the nerves, blood vessels and spinal cord that pass through the skull base. BBTC surgeons treat these tumors using innovative techniques that reduce or eliminate the need to move the brain. This minimizes injury to the brain, cranial nerves and blood vessels.

BBTC endoscopic neurosurgeons work closely with endoscopic sinus surgeons in the Head and Neck Institute to perform minimally invasive surgery for skull base malignancies and pituitary region tumors. Our Section of Skull Base Surgery is recognized internationally as one of the largest programs specializing in the management of meningiomas, slow-growing tumors that develop from the meninges, the protective covering of the brain and spinal cord. These tumors usually are benign, but they can cause numerous nervous system problems such as dizziness, vision disturbances and seizures.

Specialists in the Section of Skull Base Surgery evaluate more than 200 new meningioma patients annually. Among these, approximately 50 percent of patients are treated with surgery, 15 percent are treated with Gamma Knife radiosurgery or conventional radiation, and the remainder do not undergo immediate treatment.

In addition to its large clinical volume, the Section of Skull Base Surgery has one of the world’s most active clinical research programs in meningioma. Our skull base surgeons frequently publish research reports in leading professional journals.

Pituitary and Neuro-Endocrine Center (PNEC)

The BBTC works closely with the Endocrinology, Diabetes and Metabolism Institute; the Neurological Institute and the Department of Radiation Oncology in this center. This relationship has led to the development of integrated clinical care pathways for pre-hospital, preoperative and postoperative care for patients with pituitary tumors. New clinical care pathways have eliminated the routine use of steroids prior to surgery, allowing for a more accurate determination of postoperative pituitary adrenal activity. This also has decreased the patient’s length of stay and has maintained excellent patient outcomes.

The PNEC database provides for detailed preoperative endocrine testing, including cotrosyn stimulation, for comparison to postoperative findings.

Neuropathology

Richard Prayson, MD, who heads this section, and Susan Staugaitis, MD, PhD, perform intraoperative consultations and final pathologic diagnoses on more than 600 brain and pituitary tumor specimens each year. Nearly 550 of these specimens have been digitally captured for discussion at BBTC brain tumor boards. A panel of immunohistochemical and molecular tests is used to evaluate all glioma specimens.

Neuropsychology

Our understanding of the cognitive consequences of brain tumors and their treatment continues to expand. Much of this new knowledge is derived from the work of Michael Parsons, PhD, ABPP, a staff neuropsychologist appointed to the BBTC who focuses clinical and research attention on these issues.

We now integrate brief cognitive evaluations into the surgical program of all patients with cognitive concerns, and many patients receive baseline screenings prior to treatment.
This proactive approach lays the groundwork for coping with cognitive problems that may develop after treatment. It also reassures our patients that we have concern for the cognitive and emotional consequences of brain tumors and their overall quality of life.

Innovative research programs have sprung from the collaborative relationship between neuropsychology and the BBTC. Dr. Chao, a radiation oncologist, and Dr. Parsons have initiated an important study that is using advanced brain imaging techniques and thorough cognitive assessment to understand the consequences of brain radiation.

The study aims to identify individual differences that predict who will be at risk for cognitive problems from brain radiation and what factors protect people from those risks.

Neuroradiology

The sections of Neuroradiology and Magnetic Resonance Imaging in the Cleveland Clinic Imaging Institute continue to support the BBTC with a wide array of diagnostic capabilities and research projects. Diagnostic imaging capabilities include routine imaging, diffusion imaging and high-resolution preoperative planning studies at all of our facilities.

At main campus, we also have the capability to provide MR perfusion imaging, diffusion tensor imaging, fMRI, MR spectroscopy and positron emission tomography (PET) imaging for more advanced preoperative planning. These data can be merged with other digital imaging data sets and incorporated into the computerized neurosurgical planning.

Neuro-Oncology Social Work

Neuro-oncology social workers address any psycho-social issues that may interfere with a patient’s treatment in the BBTC. Working closely with patients and families, they address issues such as financial stress, children, home care, transportation logistics, private duty nursing, work/job issues, emotional coping, and caregiver stress. Supportive counseling is provided as needed, and an oncology psychiatrist helps assess patients for psychotropic medications that may help modulate anxiety and/or depression.

Many brain tumor patients undergo radiation therapy as part of their treatment plan. To ensure that all patients receive the support they need without duplication of services, the brain tumor social workers coordinate care between the outpatient neuro-oncology social worker and the radiation oncology social worker.

SPINE TUMOR BOARD GUIDES TREATMENT SELECTION

Making the right treatment recommendation for spine tumor patients can be complex and requires an integrated approach. Under the direction of Lilyana Angelov, MD, Head of Spinal Radiosurgery, a multidisciplinary Spine Tumor Board includes members of the Center for Spine Health; the BBTC; departments of Radiation Oncology, Neuroradiology, Surgical Pain Management and Hematology/Oncology; the Pathology & Laboratory Medicine Institute; and fellows, residents, nurses and physician assistants from multiple disciplines. Since its inception four years ago, the Spine Tumor Board has provided treatment recommendations for more than 1,300 patients.

Neuro-Oncology Nursing and Advanced Practitioners

Nurses and physician assistants specializing in the care of patients with brain tumors are an integral part of the BBTC. Our dedicated team of more than a dozen registered nurses and physician assistants provides clinical expertise in caring for patients undergoing outpatient treatment, assists patients participating in clinical trials and provides one-on-one and group teaching for patients and families.

Access to Care

All patients have access to all BBTC services through a single phone number (216.636.5860 or toll-free 866.588.2264) or through our website (www.clevelandclinic.org/braintumor). This simplifies the process of scheduling multiple appointments with various specialists in our center. The BBTC offers same-day appointments for maximum patient convenience.
**PROFESSIONAL EDUCATION**

Fulfilling our mission to advance brain tumor treatment and research through collaboration and education, the BBTC and the Department of Neurosurgery coordinated and hosted the second International Symposium on Long-Term Control of Secondary Central Nervous System Malignancies. Symposium participants had the opportunity to learn about the latest interventions and late effects associated with long-term control of CNS metastasis.

The BBTC Gamma Knife Center held three Gamma Knife Perfexion Radiosurgery training courses in 2011. Our center is one of only three in the world that provide introductory Gamma Knife training for new practitioners.

**PATIENT EDUCATION**

Kathy Lupica, MSN, CNP, and Barb Savage, LISW, facilitate the BBTC’s monthly Brain Tumor Support Group for patients, families and friends. They, along with Mary Murphy, BSN, participated in planning and attended the third annual Brain Cancer Symposium for patients and families held at the Gathering Place June 25, 2011. Glen Stevens, DO, PhD, head of Adult Neuro-Oncology, and Dr. Chao presented at the symposium.

Ms. Lupica and Ms. Savage attended the American Association of Neuroscience Nurses 43rd Annual Education Meeting in Kansas City. Shelley Ogrin, MSN, RN, CNP, presented at the 14th Annual Innovations in Neuroscience Meeting in Cleveland.

In 2011 the BBTC continued B-AwareSM, a public education program that raises awareness of brain metastases and their signs and symptoms. The program emphasizes that brain metastases are treatable, but early detection is critical. The campaign includes a toll-free number (866.223.8100) and a website for patients (clevelandclinic.org/b-aware).

Ms. Lupica and Gail Ditz, RN, BSN, presented at the American Association of Neuroscience Nurses 43rd Annual Education Meeting in Kansas City. Shelley Ogrin, MSN, RN, CNP, presented at the 14th Annual Innovations in Neuroscience Meeting in Cleveland.

**FELLOWSHIPS**

The BBTC offers two neurosurgical oncology fellowships. A two-year combined clinical and laboratory research fellowship provides exposure to the design and operation of clinical trials as well as opportunities to contribute to neuro-oncology professional journals. Fellows are expected to participate in the design, application to the Institutional Review Board and management of new clinical trials during this fellowship and to produce clinical presentations and reports.

The second fellowship is offered through the Section of Skull Base Surgery. It offers in-depth experience in the highly specialized surgical techniques used to access deep-seated, difficult-to-reach lesions by anatomic displacement or extensive removal of the base of the skull.

**Fellows, 2002 – Present**

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<td>Dae Lee, MD</td>
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<td>Burak Sade, MD</td>
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<td>Jae Sung Park, MD</td>
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<td>Soichi Oya, MD</td>
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<td>Bjorn Lobo, MD (Enfolded Fellowship &amp; Residency)</td>
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<td>Pablo Recinos, MD</td>
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<td>Neda Hashemi-Sadraei, MD</td>
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<td>Lizbeth Robles-Irizarry, MD</td>
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### Appendix A

#### Clinical Trials

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<tr>
<td>CC385</td>
<td>CASE 4107</td>
<td>Clinical Study to Assess Entry of Chemotherapeutic Agents into Brain Metastases in Women with Breast Cancer</td>
<td>Peereboom</td>
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<td>CC559</td>
<td>RTOG 0614</td>
<td>A Randomized, Phase III, Double-Blind, Placebo-Controlled Trial of Memantine for Prevention of Cognitive Dysfunction in Patients Receiving Whole-Brain Radiotherapy</td>
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<td>CC845</td>
<td>CASE 4309</td>
<td>A Phase I/II Trial of SRS Plus Bevacizumab in patients with recurrent/progressive GBM</td>
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<td>CC578</td>
<td>NABTT 0703</td>
<td>Phase I/II study of poly (ADP-ribose) polymerase-1 (PARP-1) inhibitor BSI-201 in patients with newly diagnosed malignant glioma</td>
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<td>CC669</td>
<td>NABTT 0801</td>
<td>A Phase I/II Trial of Temozolomide and ABT-888 in Subjects with Newly Diagnosed Glioblastoma Multiforme</td>
<td>Stevens</td>
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<td>CC739</td>
<td>RTOG 0825</td>
<td>A Phase III Double-Blind Placebo-Controlled Trial of Conventional Concurrent Chemoradiation and Adjunct Temozolomide Plus Bevacizumab versus Conventional Concurrent Chemoradiation and Adjunct Temozolomide in Patients with Newly Diagnosed Glioblastoma</td>
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<td>CC819</td>
<td>RTOG 0539</td>
<td>Phase II Trial of Observation for Low-Risk Meningiomas and of Radiotherapy for Intermediate- and High-Risk Meningiomas</td>
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<td>CC813</td>
<td>ABTC 0904</td>
<td>A Biomarker and Phase II Study of GDC-0449 in Patients with Recurrent Glioblastoma</td>
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<td>CC828</td>
<td>ABTC 0903</td>
<td>A Phase Ib Study of Cediranib in Combination with Cilengitide in Patients with Recurrent Glioblastoma</td>
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<td>CC827</td>
<td>ABTC 0902</td>
<td>Phase I/II Study of Vorinostat (Suberoylanilide Hydroxamic Acid [SAHA]), Temozolomide, and Radiation Therapy in Patients with Newly Diagnosed Glioblastoma</td>
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<td>CC879</td>
<td>EXEL 2310</td>
<td>A Phase I Dose-escalation Study of XL765 in combination with Temozolomide in Subjects with malignant Gliomas</td>
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<td>CC877</td>
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<td>An Open Label, Phase 2 Study Evaluating the Safety and Efficacy of IMC-3G3 or IMC-1121B in Patients with Recurrent Glioblastoma Multiforme</td>
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<td>CC869</td>
<td>E3F05</td>
<td>Phase III Study of Radiation Therapy with or without Temozolomide for Symptomatic or Progressive Low-Grade Gliomas</td>
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<td>CC949</td>
<td>TOG 1309</td>
<td>A Phase 1 Ascending Dose Trial of the Safety and Tolerability of Toca 511 in Patients with Recurrent Glioblastoma Multiforme</td>
<td>Vogelbaum</td>
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<td>CC1009</td>
<td>ABTC 0906</td>
<td>A Phase II and Pharmacodynamic Trial of RO4929097 for Patients with Recurrent/Progressive Glioblastoma</td>
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<td>CC931</td>
<td>NOVO 1308</td>
<td>A Prospective, Multi-center Trial of NovoTTF-100A Together with Temozolomide Compared to Temozolomide Alone in Patients with Newly Diagnosed GBM</td>
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<td>CC00118</td>
<td>ICT 1310</td>
<td>A Randomized, Double-blind, Controlled Phase Ib Study of the Safety and Efficacy of ICT-107 in Newly Diagnosed Patients with Stage IV Glioblastoma Multiforme (GBM) Following</td>
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<td>CC00195</td>
<td>TOG1311</td>
<td>A Continuation Protocol for Patients Previously Enrolled in a Study of Toca 511</td>
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<td>11-1091</td>
<td>CASE 1311</td>
<td>A Phase 2 Comparative Study of 5-Aminolevulinic Acid (5-ALA) &amp; Intraoperative MRI (iMRI) to Enhance Completeness of Resection of Glioblastoma</td>
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<td>7936</td>
<td>NABTT 0306</td>
<td>A Safety Run-In/Randomized Phase II Trial of EMD 121974 in Conjunction with Radiation Therapy in Patients with Newly Diagnosed Glioblastoma Multiforme NCI #: PI: Nabors</td>
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<td>8314</td>
<td>NABTT 0304</td>
<td>A Phase II Trial of Talampanel in Conjunction with Radiation Therapy with Concurrent and Adjunct Temozolomide in Patients with Newly Diagnosed Glioblastoma Multiforme</td>
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<td>Phase III Randomized Trial of the role of Whole Brain Radiation Therapy in Addition to Radiosurgery in Patients with One to Three Cerebral Metastases</td>
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<td>CC238</td>
<td>RTOG 0227</td>
<td>A Phase II/I Study of Pre-Irradiation Chemotherapy With Methotrexate, Rituximab, Temozolomide And Post-Irradiation Temozolomide For Primary Central Nervous System Lymphoma</td>
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<td>CC186</td>
<td>MAYO 1306</td>
<td>Phase II Study of AZD2171 in Adult Patients with Neurofibromatosis Type I and Extensive Plexiform &amp; Paraspinal Neurofibromas (Mayo Protocol #MC047F; NCI Protocol #7133)</td>
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<td>CC243</td>
<td>NABTT 0602</td>
<td>A Phase I, Open Label Study of AT-101 Plus Radiotherapy &amp; Temozolomide &amp; of AT-101 Plus Adjuvant Temozolomide for Patients with Newly-Diagnosed Glioblastoma Multiforme</td>
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<td>CC436</td>
<td>NABTT 0702</td>
<td>A Phase 2 Study of R(-)-gossypol (Ascenta's AT-101) in Recurrent Glioblastoma</td>
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<td>CC429</td>
<td>MGI 1307</td>
<td>A Phase II, Multicenter, Exploratory Study, Evaluating the Treatment Effect of Surgery Plus GLIADEL Wafer in Patients with Metastatic Brain Cancer</td>
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<td>CC526</td>
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<td>A Prospective First-in Man (FIM) Safety Trial of the AutoLITT Laser Treatment of Recurrent/Progressive Brain Tumors</td>
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<td>CC396</td>
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<td>An open-label, multicenter, Phase II study to evaluate the activity of Patupilone (EPO906), in the treatment of recurrent or progressive brain metastases in patients with NSCLC</td>
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<td>CC582</td>
<td>BRMY 1308</td>
<td>Phase 1, Open Label, Multi-Center Study to Evaluate the Safety and Tolerability of CT-322 Administered in Combination with Focal Brain Radiotherapy and Temozolomide to Subjects with Newly Diagnosed Glioblastoma Multiforme</td>
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<td>CC00017</td>
<td>MDCC 1310</td>
<td>Two Phase I Studies, Followed by a Randomized Phase 2 Study of RO4929097 Combined with CNS Radiotherapy in Patients with Brain Metastases from Breast Cancer Whose Tumors are Estrogen Receptor Negative</td>
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<td>A Phase II Study of Temozolomide-Based Chemotherapy Regimen For High Risk Low-Grade Gliomas</td>
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<td>A Phase III Trial Comparing Whole Brain Radiation and Stereotactic Radiosurgery Alone Versus with Temozolomide or Gefitinib in Patients with Non-Small Cell Lung Cancer and 1-3 Brain Metastases</td>
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<td>CC050</td>
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<td>A Phase II Trial of Radiation Plus Temozolomide Followed by Adjuvant Temozolomide and Poly-ICLC in Patients with Newly Diagnosed Glioblastoma Multiforme</td>
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<td>RTOG 0525; Phase III Trial Comparing Conventional Adjuvant Temozolomide with Dose-Intensive Temozolomide in Patients with Newly Diagnosed Glioblastoma</td>
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<td>CC185</td>
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<td>A Phase II Trial of Patupilone in Patients with Brain Metastases from Breast Cancer</td>
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<td>CC126</td>
<td>NOVO 1306</td>
<td>A Prospective, Multi-center Trial of NovoTTF-100A Compared to Best Standard of Care in Patients with Progressive or Recurrent GBM</td>
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<td>CC140</td>
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<td>Open-Label Phase I/Phase II Study of Intravenous Infusion of Tetra-o-Methyl Nordihydroguaiaretic Acid (EM-1421) in Subjects with Recurrent High Grade Glioma</td>
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<td>CC222</td>
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<td>A Feasibility Assessment and a Phase II/III Trial of MLN518 for Treatment of Patients with Recurrent Glioblastoma</td>
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<td>CC432</td>
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<td>Phase I/II of Hydroxychloroquine in Conjunction w/RT</td>
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<td>CC603</td>
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<td>Phase II Trial of Sunitinib As Maintenance Therapy After Stereotactic Radiosurgery in Patients with 1-3 Newly Diagnosed Brain Metastases</td>
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Appendix B

PUBLICATIONS

JOURNAL PUBLICATIONS


Appendix B

BOOKS, WHOLE


BOOK CHAPTERS


The Burkhardt Brain Tumor and Neuro-Oncology Center continues to grow in volume of procedures. In 2011, our physicians performed 503 stereotactic radiosurgery (Gamma Knife and Novalis) and 491 surgical procedures, a combined 65 percent increase compared with 2001. Total outpatient visits increased by 358 percent over the past 11 years.

New patient visits have doubled since 2001.

Over the past 11 years, the number of patients on research trials has increased from 81 to 310, or 284 percent.
The Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center is a nationally recognized leader in the diagnosis and treatment of primary and metastatic tumors of the brain, spine and nerves. The center, part of the multidisciplinary Neurological Institute, is internationally known for superior diagnosis and treatment of neurological disorders ranging from the common to the most complex. More than 300 specialists combine clinical expertise, academic achievement and innovative research for the benefit of adult and pediatric patients.

The Neurological Institute is one of 26 institutes at Cleveland Clinic, a not-for-profit academic medical center ranked among the nation’s top hospitals (U.S. News & World Report), where nearly 3,000 physicians in 120 specialties collaborate to give every patient the best outcome and experience.

clevelandclinic.org/braintumor