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Letter from the Director

The Brain Tumor and Neuro-Oncology Center (BTNC) of Cleveland Clinic was established in 2001, with a novel organization that has helped propel us to the forefront among the leading brain tumor programs in the nation. We are serving more patients than ever; expanding our services and improving patient satisfaction; attracting world-class physicians and scientists; making giant leaps in research and discovery; and acquiring much-needed funding, particularly philanthropic support.

In 2008, among the hundreds of clinical studies under way, the BTNC led 26 new clinical studies that were investigator initiated, in partnership with industry or through consortia. Among these was the first-ever human use of a minimally invasive laser treatment for glioblastoma – performed as part of a collaborative trial with the Case Comprehensive Cancer Center and University Hospitals Case Medical Center.

Collaborating with and being in the Taussig Cancer Institute, the largest cancer program in Ohio, the BTNC has access to the institute’s clinical and research resources as well as the opportunity to interact with other healthcare professionals who deal with cancer patients daily. Using innovative therapy and a multidisciplinary structure – a model of organization that continues to attract national and international interest – we provide a team approach to individualized care. We look forward to improving care as we continue to measure our performance.

Gene H. Barnett, MD, FACS
Director, Brain Tumor and Neuro-Oncology Center
Faculty and Key Personnel

Brain Tumor and Neuro-Oncology Center Faculty

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*Denotes joint appointment
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Executive Director of Development,
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Executive Director of Development,
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Medical Secretary
Janette Collazo
Medical Secretary
Peggy Evans
Medical Secretary
Cassandra Holliday
Medical Secretary
Tamika Smith
Medical Secretary

Taussig Cancer Institute
John Pellecchia
Grant Administrator
Denise Connor
Research Finance Manager
Kristie Summers
Division Research Administrator
Deb Johnson
Research Accountant

Nursing/Physician Assistants
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BTNC Nurse Manager
Cathy Brewer, RN
Gail Ditz, RN, BSN
Carla Duvall, MSN, CNP
Michele Gavin, MPAS, PA-C
Betty Jamison, RN, BSN
Kathy Lupica, MSN, CNP
Mary Miller, RN, BSN
Mary Murphy, RN
Shelley Ogrin, MSN, RN, CNP
Carol Patton, RN
Rachel Perez, RN, BSN
Sherry Soeder, MSN, CNP
Laural Turo, RN, BSN
Executive Summary

Cleveland Clinic Brain Tumor and Neuro-Oncology Center enjoyed a year of substantial accomplishment in 2008.

Record-Setting Clinical and Financial Performance:
- 7,943 outpatient visits
- 936 surgical, Gamma Knife® and Novalis® procedures
- Increase of 150% new patient visits, 366% total outpatient visits, 23% surgical cases and 91% Gamma Knife cases since program’s inception in 2001
- Largest market share in Ohio
- 21% increase in net revenue and 85% increase in contribution margin over 2007

Solid Research Revenue and Philanthropic Support:
- Funding through three federal grants
- $1.5M in philanthropic support since 2007 and $14.6M since inception

Pace-Setting Clinical Programs:
- World’s first human treatment of brain tumor using AutoLITT® thermal therapy system (see cover figure)
- Advance navigation using DTI and fMRI planning and intraoperative visualizations
- Compact MRI with development of high-field interventional MRI operating room
- Leader in convection-enhanced delivery of advanced agents to brain tumors
- Second Gamma Knife Perfexion unit in North America – 317 cases in 2008
- Leader in spinal radiosurgery – 74 procedures performed in 2008, and more than 200 cases since program inception in 2004
- Integration of neuropsychology into clinical program

Robust Clinical Research:
- Completing membership in NCI-sponsored New Approaches to Brain Tumor Therapy (NABTTT) consortium
- Charter member of NCI-sponsored Adult Brain Tumor Consortium (ABTC), commencing in 2009
- Leadership in national brain tumor organizations
- Dr. Vogelbaum Scientific Program Chair of 2008 Society of Neuro-Oncology Meeting

Laboratory Research:
- Recruitment of Jeremy Rich, MD, as Chair of Genomics Institute. Dr. Rich, a world-renowned expert on brain tumor stem cells, joined the professional staff in September 2008.
- Recruitment of Candece Gladson, PhD, as Head of Brain Tumor Laboratory Research in the Department of Cancer Biology of Cleveland Clinic Lerner Research Institute. Dr. Gladson joined the staff in January 2009.
- Primary labs and collaborations performing cutting-edge basic and translational research

Education – Local, Regional, National and International Presence:
- Hosted Second International Symposium on Stereotactic Body Radiation Therapy and Stereotactic Radiosurgery
- Hosted Pituitary Disease Symposium in April
- Hosted joint meeting with Mexican Neurosurgical and Neuro-Oncology Societies in November at Los Cabos, Mexico
- Hosted four Gamma Knife hands-on courses

Publishing Our Accomplishments:
- BTNC staff published 38 journal articles and two book chapters in 2008
Brain Tumor and Neuro-Oncology Center – Overview

A Team Approach to Individualized Care

Cleveland Clinic Brain Tumor and Neuro-Oncology Center (BTNC) is a national leader in the diagnosis, treatment and research of brain tumors. The unique administrative structure of the BTNC allows our multidisciplinary team of physicians and scientists to focus almost exclusively on brain tumors, facilitating opportunities for our staff to participate in international research protocols, share information about the latest developments in the field and combine therapeutic approaches from a number of disciplines. The result is the ability to bring the most promising new treatments to the clinical realm in an environment that facilitates individualized patient care.

The BTNC has been a member of the prestigious New Approaches to Brain Tumor Therapy (NABTT) consortium for more than seven years. The primary objective of the National Cancer Institute-sponsored NABTT consortium is to improve the therapeutic outcome for adults with primary brain tumors while sharing human brain tumor specimens and clinical and laboratory data to facilitate additional research pertaining to basic biology and neuro-pharmacology of new treatments. To qualify for NABTT membership, an institution must possess strong clinical and research programs for adult brain tumors, expert multidisciplinary clinical teams, extensive laboratory and clinical resources, and the ability to conduct high-quality, clinically relevant trials. In 2008, we were honored to be selected as a charter member of the new Adult Brain Tumor Consortium, which supersedes the NABTT consortium in 2009.

Building on the strong tradition of excellence and innovation established by members of the BTNC team, the future of clinical application and ongoing research at Cleveland Clinic is both bright and exciting. We aim to streamline the process of bringing potentially groundbreaking therapeutic agents from the laboratory to the patient, making new chemotherapeutic agents, radiosurgical techniques and surgical procedures available more quickly, while maintaining the highest scientific standards for both efficacy and safety.
Clinical and Financial Performance – 2008


Higher Patient Volume

Between 2001 and 2008, the BTNC experienced an increase in new patient volume of 150 percent; an increase in total outpatient visits of 366 percent; an increase in surgical cases of 32 percent; and an increase in Gamma Knife cases of 92 percent.

In 2004, BTNC physicians began performing Novalis radiosurgery, starting with only three cases. By 2008, our staff performed 82 of these procedures.

Overall in 2008, BTNC physicians recorded 7,925 outpatient visits and performed 974 surgical and radiosurgical procedures.

Larger Market Share

The BTNC maintains the highest market share in the “Cuyahoga County,” “21-county” and “state of Ohio” markets, and continues to increase dominance over its closest competitor. Future initiatives focus on increasing market share locally, regionally and nationally.

Financial Performance

Increased Revenue Between 2002 and 2008, gross revenue increased 178 percent; net revenue increased 111 percent; and contribution margin increased 79 percent.
Since 2006, generous supporters have contributed an additional $1.6 million in outright gifts, pledges and estate bequests. Of special note are an estate gift from long-time BTNC benefactor, the late Mel Burkhardt, annual golf tournament fundraisers held by Karen Wilson and ongoing research support provided by the Wolf Family Foundation. This foundation of philanthropic support has proven critical to the BTNC’s efforts to advance brain tumor treatment and research.

In addition to financial support, friends also contribute their time and invaluable service as members of the Neurological Institute and Taussig Cancer Institute National Leadership Boards. The BTNC is grateful for the continued loyalty of many members who served on the former Brain Tumor Institute Leadership Board. Many have continued their service on one or both of these boards as Cleveland Clinic has moved to a multidisciplinary institute model of medicine which positions the BTNC as part of the Neurological Institute with strong collaborative ties to the Taussig Cancer Institute. We are especially grateful to former Brain Tumor Institute Leadership Board Chair L.B. McKelvey and member Karen Wilson, who have joined the Neurological Institute Leadership Board.

All development activities supporting the BTNC are coordinated by Jason Gray, Associate Chairman of Institute Development, Institutional Relations and Development, and Laura Robinson, Senior Director of Development, Neurological Institute. In collaboration with physicians and healthcare professionals and the Taussig Cancer Institute development team, the fundraisers and leadership boards drive efforts to increase awareness and provide opportunities for friends to support priority research and clinical initiatives.
## Benefactors

### Partners in Neuro-Oncology

The Brain Tumor and Neuro-Oncology 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.

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<tr>
<th>Melvin H.* and Rose Ella* Burkhardt</th>
<th>Mr. and Mrs. Lucius B. McKelvey</th>
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<td>Robert W. and Kathryn B. Lamborn</td>
<td>Ms. Karen Wilson</td>
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<td>Alfred* and Norma Lerner</td>
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*Deceased

### 2008 Benefactors

The Brain Tumor and Neuro-Oncology Center is pleased to acknowledge the following friends whose 2008 giving in support of our mission totaled $1,000 or more.

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<th>The James &amp; Coralie Centofanti Charitable Foundation</th>
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<td>Candy and Eddie DeBartolo and Family</td>
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<td>Thomas N. Detesco, MD</td>
<td>Mrs. Jodi O’Neill</td>
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<td>The Carmel M. &amp; John G. Whitman Foundation</td>
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<tr>
<td>Dennis M. Moody, DDS</td>
<td>Dr. John York and Ms. Denise DeBartolo York</td>
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### Tommy Detesco Fund

The BTNC team is especially indebted to Dr. Thomas N. Detesco, who established the Tommy Detesco Fund in 2007 in memory of his son Tom, who passed away at 32 years old after a long battle with brain cancer. The fund supports adolescent and young adult brain tumor research at the BTNC. Since its establishment, the fund has received more than $350,000 in gifts and pledges, with a goal of $2 million. More than half of those who gave $1,000 or more to the BTNC in 2008 designated their gifts to support the Tommy Detesco Fund.
Clinical Programs

The BTNC offers comprehensive care for patients with benign or malignant brain tumors. Our multidisciplinary approach involves the closely coordinated efforts of multiple specialists working together daily, most of whom treat only patients with brain tumors. This degree of subspecialization has allowed us to contribute to development of new, cutting-edge investigational treatments, including the use of targeted immunotoxins and so-called “small molecule therapies” (SMTs) such as erlotinib and sunitinib. Newer agents that cross the blood-brain barrier, such as patupilone, are being tested in patients with brain metastases. These, along with the expanded routine use of molecular and chromosomal testing to guide individual patient management, help put the BTNC at the forefront of individualized care and the molecular genetic management of brain tumors.

Methods for both surgical and nonsurgical treatments of life-threatening tumors are advanced by medical innovations in the areas listed below. Among the innovations is the use of several modalities of therapy in multidisciplinary, individualized care of the patient with a brain tumor.

- **Advanced Surgical Navigation** – computer-guided surgery using a three-dimensional software configuration capable of employing diffusion tensor imaging (DTI) and functional magnetic resonance imaging (fMRI) data
- **Intraoperative MRI** – navigational guidance and monitoring of tumor resection
- **Multiple Radiosurgery Options** – Gamma Knife for single-session cranial stereotactic radiosurgery; Novalis System for cranial radiosurgery in several sessions and spinal radiosurgery
- **Fractionated Radiotherapy** – widespread exposure of the brain and tumor to repeated low doses of radiation
- **Brachytherapy** – direct implantation of a radiation source (solid or liquid) within a tumor site
- **Chemotherapy/Growth Modifiers** – traditional anti-tumor drugs as well as testing of new agents targeted at specific tumor molecules
- **Immunotherapy** – turning the patient’s immune system against tumor cells or using immunologically targeted toxins
- **Convection-Enhanced Delivery (CED)** – the slow, continuous infusion of drugs through the brain to treat certain brain tumors. Used both in the laboratory and for patients, it permits treatment with agents that would be too toxic to the body if delivered conventionally.
- **Laser Interstitial Thermal Therapy (LITT)** – use of a specialized laser probe to “cook” certain brain tumors from the inside, and monitoring the procedure using special MRI techniques

Medical Neuro-Oncology

Neuro-oncologists, medical oncologists, neurosurgical oncologists, radiation oncologists, neuropathologists, neuroradiologists and BTNC nurses attend daily clinics and twice-weekly tumor boards. This cooperative approach, proved in more than a decade of use, provides for consensus management plans that are individualized and focused on the best mix of medical, surgical and radiotherapy treatment of patients with both benign and malignant tumors affecting the brain and spinal cord. In addition to conventional treatments, innovative clinical studies – some of which were developed at Cleveland Clinic – are available, and others are performed as part of multicenter trials.

Members of the medical neuro-oncology team also provide long-term surveillance and medical management of patients. These specialists pay particular attention to the neurocognitive impact of brain tumors, and play an important role in the management of anti-seizure medications. For example, Dr. Glen Stevens received
external funding to evaluate seizure control and side effects associated with the anticonvulsant levetiracetam in brain tumor patients.

Neurosurgical Oncology

Pioneers in computer-assisted stereotactic techniques for brain tumors since the mid-1980s, BTNC surgeons extended the scope of operable brain tumors by using techniques such as frame or frameless stereotaxy (to provide a fixed frame of reference to assist with computerized navigation for locating brain tumors), laser surgery, skull base techniques, microsurgery, endoscopic surgery, computer-assisted rehearsal of surgery, intraoperative MRI, radiation implants and radiosurgery. The development of precision surgical navigation systems by Cleveland Clinic’s Center for Computer-Assisted Neurosurgery has resulted in substantial reductions of wound and neurologic morbidity, length of surgery, hospital costs, and length of stay for many benign and malignant brain tumor surgeries. The interest in surgical navigation continues as the Department of Neurosurgery uses navigation equipment from Z-KAT, Medtronics/Stealth and BrainLAB. The ability to plan and navigate using specialized imaging techniques such as diffusion tensor imaging (DTI) fiber tracking and functional MRI (fMRI) allows us to see the critical brain pathways and surface regions, thus making brain tumor surgery even safer, and to extend what is truly operable.

The BTNC continued the pursuit of cutting-edge technology with its acquisition of the second-generation compact intraoperative MRI, the PoleStar N20. The device weighs only 1,300 pounds – a fraction of the weight of conventional units. During surgery, the device is stowed below the operative field, allowing use of many conventional surgical instruments. When imaging is required, the magnets are raised into position, flanking the patient’s head for scans that range in time from about one to seven minutes. When not required during surgery, the imager is placed in a magnetically shielded cage in the corner of the room, allowing full use of the room for conventional procedures. We were one of the first sites in the world to have the first generation of the PoleStar system, and have been viewed as pioneers in the application of intraoperative MRI to neurosurgical procedures. In conjunction with the radiological Imaging Institute and neuroradiology, we are developing a new high-field (1.5 Tesla) interventional MRI suite/operating room to extend what can be done and monitored with real-time MRI techniques.

Local Therapies

Malignant gliomas are invasive tumors. While the portion of the tumor that forms a mass lesion can often be removed surgically, surgery is not regarded as a curative treatment, as the invasive portion of the tumor inevitably remains behind. While the density of invasive tumor cells may be greatest at the resection margin, tumor cells can be found centimeters away, even beyond the limits of the T2/FLAIR abnormality seen on MRI. It has been reported that as many as 80 percent to 90 percent of tumor recurrences occur within two centimeters of the resection cavity, and the shrinking field technique of radiation therapy was designed to provide the highest radiation dose to the area around the tumor cavity. Hence, there is great interest among neurosurgical oncologists in use of other localized and regionalized therapies to treat the margins of the tumor resection cavity as well as the tumor-infiltrated brain distant from the cavity.

The BTNC was the first in the world to use a new laser-based system in a human for the minimally invasive treatment of a brain tumor. This AutoLITT (laser interstitial thermal therapy) system, developed by Monteris Medical (Winnipeg, Canada), “cooks” or coagulates tumors by use of a special laser probe, precisely directed into the tumor, with the heating process monitored by specialized software and thermal MRI techniques (see cover figure). Dr. Gene Barnett leads this trial 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 interventions.

A recently investigated approach for both local and regional drug delivery involves convection-enhanced delivery (CED). In contrast to implanted chemotherapy wafers, CED relies on positive pressure infusion to produce a more widespread and uniform volume of drug delivery. This technique requires the implantation of temporary catheters, which can be directed to treat specific regions of the brain suspected of being infiltrated by tumor, as determined by MRI. Novel classes of targeted drugs, which cannot be administered systemically due to breakdown or toxicity, have been developed for direct delivery to the brain via CED. While early trials of this technique have shown evidence of efficacy, Phase III evidence does not yet exist to support this approach. The field of CED remains in an early stage of development, and new types of both catheters and drugs are being developed to optimize efficacy of this approach. The BTNC has been a recognized leader in the clinical development of CED. The BTNC has participated in several CED multicenter national and international trials, one of which was designed and led by a BTNC neurosurgeon. Furthermore, the BTNC has hosted the only international symposia focused on CED. Several new trials are being developed and will be led by BTNC neurosurgeons.

Radiation Neuro-Oncology

Radiation oncologists, focusing on the specific problems of brain and spinal cord tumors, offer both traditional and innovative treatments to ensure patients access to a number of technologies. In 1989, Cleveland Clinic’s radiosurgery program was the first in Ohio to treat patients with state-of-the-art noninvasive ablative therapy, using a modified linear accelerator. Since 1997, a number of technologies have been introduced, including 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 whose general health may not be sufficient to withstand a protracted microsurgical procedure.

A team of personnel including neurosurgeons, radiation oncologists, radiation physicists and radiation therapists provides treatment. Gamma Knife radiosurgery generally requires a single one- to two-hour treatment in which 192 beams of gamma rays are focused at multiple points throughout the target, with the aim of matching the delivered radiation to the shape of the tumor. Thus, the radiation’s destructive potential is concentrated in the tumor, and falloff in adjacent tissue is exceedingly steep, minimizing damage to tissue lying in the entry or exit pathways. Because of this precise focusing ability, aggressive high-dose radiation can be delivered to stabilize, shrink or destroy some lesions – even those deep in the cerebral hemispheres or brain stem.

The past year has been a successful one for the Gamma Knife Center. In 2007, our Gamma Knife equipment was upgraded to the latest Perfexion system, which is a complete redesign of the previous Gamma Knife and offers greater flexibility and safety. In 2008, we performed 317 Gamma Knife radiosurgery cases for a number of indications, which represented our most productive year ever. In addition, we presented a number of papers at national and international meetings, highlighting our center’s results.

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

The Novalis System further increases our capabilities within radiation oncology and allows for radiosurgery and fractionated radiosurgery treatments for
neuro-oncology patients, using image guidance. This technology gives us the ability to treat lesions near critical structures, such as the optic nerves and chiasm, as well as re-treat some patients who have undergone conventional radiotherapy. In general, Gamma Knife is used for single treatments of focused radiation that conforms to the shape of small tumors or lesions, while Novalis delivers fractionated conformal treatment for larger malignant or benign tumors. Although Novalis was originally developed to treat brain tumors, Cleveland Clinic physicians recognized its potential for treating extracranial tumors, particularly primary and metastatic spinal tumors that are difficult to treat due to their proximity to critical structures. In 2007, we became one of the busiest spine radiosurgery programs in the nation to use the Novalis platform.

In addition to the Gamma Knife, Novalis System and linear accelerators, we offer IORT with the INTRABEAM device, a 50 kVp contact unit that is placed in the resection cavity. We have an ongoing Phase II trial evaluating the use of INTRABEAM for patients with a single brain metastasis that has been resected.

A number of clinical trials sponsored through the Radiation Therapy Oncology Group (RTOG), NABTT and various pharmaceutical companies are offered here. Since 1998, the department has been a leader in radiation sensitizer trials using motexafin gadolinium and efaproxiral. Dr. John Suh was the principal investigator for the international Phase III confirmatory study using efaproxiral for women with brain metastases from breast cancer. Dr. Samuel Chao’s research interest includes radiation necrosis, a potential complication of radiation treatment, and treatment of pediatric brain tumors. Both have given a number of national and international talks regarding the treatment of brain tumors with radiation therapy and radiosurgery.
Section of Metastatic Disease

Surgery

Surgery, in addition to whole brain radiotherapy, has been shown to be more effective than radiotherapy alone for patients with a single brain metastasis. Even in patients with multiple brain metastases, surgical resection leads to survival comparable to those patients with single resected lesions. Pioneers in contemporary computer-assisted neurosurgery, BTNC neurosurgeons routinely use minimal access techniques to remove one or more brain metastases, with minimal morbidity and short hospital stays. Also, BTNC clinical researchers are investigating the role of intraoperative chemotherapy or radiotherapy after resection, in the hope of obviating the need for whole brain radiotherapy.

Today, surgery may be part of a comprehensive management plan, with other techniques brought to bear on additional brain metastases not amenable to radiotherapy. Beyond radiotherapy, staged therapy options include stereotactic radiosurgery, intra-arterial chemotherapy with or without blood-brain barrier disruption, and newer systemic chemotherapies.

Radiosurgery

Cleveland Clinic’s radiosurgery program is the oldest in Ohio and has distinguished itself with its clinical, educational and research programs. We are one of only three centers in the world certified by the manufacturer of the Gamma Knife to train new users of this “gold standard” of radiosurgery. Since we started our Gamma Knife in 1997, we have treated more than 2,600 cases with various models of the Gamma Knife. In 2007, we became the second program in the United States to treat with the Perfexion unit, and we recently started an upgrade course for those using the Perfexion model. In addition, we have published extensively on our results, written numerous papers on Gamma Knife radiosurgery, and presented at many national and international meetings.

Our most common indication for Gamma Knife is brain metastases, which are ideally suited for treatment with stereotactic radiosurgery. Because these tumors are typically small and spherical, and because they displace, rather than infiltrate, normal brain tissue, the Gamma Knife has become our preferred strategy to treat brain metastases. Results from radiosurgery appear comparable to those achieved by surgery with radiotherapy, and allow for effective treatment even of surgically inaccessible tumors. Radiosurgery may also reduce the chance of leptomeningeal spread as a result of surgery for certain tumor types.

So-called “radio-resistant” tumor types (e.g., melanoma, renal cell carcinoma) respond as well to stereotactic radiosurgery as do “radio-sensitive” tumors. Neurologic morbidity is low when dosing is prescribed at levels set by the Radiation Therapy Oncology Group, of which Cleveland Clinic is an active member. Cognitive side effects are minimal, as the treatment is confined to small brain regions.

In addition to Gamma Knife radiosurgery, the Department of Radiation Oncology offers other stereotactic radiation options with the Novalis BrainLab unit and Synergy-S unit. Both these units provide precision radiation delivery through the use of image guidance and micro multileaf collimators. The department has been designated a “center of excellence” in the use of Novalis and has very active programs in spine, brain and lung radiosurgery.

Treatment with Novalis is indicated for those patients whose brain tumors are not ideal for Gamma Knife radiosurgery. In addition, Novalis can be used for extracranial sites such as metastatic spinal tumors and prostate and lung cancers. Since adding the Novalis System to its arsenal of radiosurgery programs four years ago, the department has treated more than 700 patients, with anatomic treatment sites including the brain, spine, lung, kidney and bone.
Chemotherapy
An exciting area of investigation is the use of small targeted molecules to treat a variety of malignancies. As the molecular characterization of various tumors improves, investigational drugs that target specific molecular pathways may play an increasing role in the management of brain metastases and even leptomeningeal disease. The use of these agents and appropriate modes of delivery are and will continue to be a major thrust of BTNC clinical and laboratory research.

Systemic cancers that are chemotherapy sensitive often take refuge in the brain, despite systemic control, as most commonly used chemotherapies have poor penetration through the blood-brain barrier. Management of such tumors may take several forms. Patients with metastatic breast cancer to the brain with tumors that are estrogen-receptor positive may respond to hormone therapies. Other agents that have activity against breast cancer brain metastases include capecitabine, methotrexate and lapatinib. One multicenter clinical trial led by the BTNC examines patupilone, an epothilone in women with breast cancer brain metastases. Alternatively, temozolomide, a relatively new orally administered methylating agent, has excellent penetration into the brain and may be considered for some patients with brain metastases from non–small-cell lung cancer or melanoma. The BTNC is participating in a clinical trial of patupilone for patients with non–small-cell lung cancer brain metastases. More intensive treatment includes use of chemotherapy injected directly into the carotid vertebral arteries, at times using hypertonic mannitol to disrupt the blood-brain barrier from preventing active agents from reaching adequate concentrations in brain metastases.

Spinal Radiosurgery
Metastatic bone pain is the most common pain syndrome encountered in cancer patients, and develops in 60 percent to 85 percent of patients with solid tumors. If the metastases involve the spine, there can be disabling pain and destruction of the vertebral body, leading to spinal instability, compression of the spinal cord or nerve roots and, ultimately, neurological dysfunction and paralysis. Both early detection and appropriate intervention are essential to minimize the sequelae of spinal metastases, thereby maximizing patient function and quality of life.

Cleveland Clinic’s Stereotactic Spine Radiosurgery (SRS) program was established in 2006 as the first spine radiosurgery program in Ohio. It is regarded as one of the pioneering programs in the country to routinely offer this outpatient treatment modality using Novalis Shaped Beam Surgery technology. This technique allows a focused radiation dose to be delivered selectively to the tumor, while sparing the adjacent normal structures. It results in rapid and effective pain and tumor control with minimal risk of side effects. Stereotactic spinal radiosurgery has thus revolutionized the treatment of malignant spine tumors and many benign tumors as well. Our experience with radiosurgery, either as single or multimodal therapy, demonstrates that this treatment is an effective option for patients with spine lesions. To date, we have treated more than 200 spine tumors, with more than 85 percent of patients with pain experiencing clinically significant relief, and local tumor control in 90 percent of patients with a single outpatient noninvasive treatment.

Spine radiosurgery is, however, just one component of a full spectrum of standard and advanced treatment options currently available at Cleveland Clinic for the treatment of patients with spine tumors. Others 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. Making the right treatment recommendation for spine tumor patients can be complex and requires a well-integrated approach. Under the direction of Dr. Lilyana Angelov, a multidisciplinary Spine Tumor Board was established, including members of the Center for Spine

Clinical Programs (continued)
Health; the Brain Tumor and Neuro-Oncology Center; departments of Radiation Oncology, Neuroradiology, Pathology, Surgical Pain Management and Hematology/Oncology; as well as fellows, residents, nurses and physician assistants from multiple disciplines. This group meets weekly, and has developed a coordinated, multifaceted approach to spine tumor patients. Since its inception two years ago, the Spine Tumor Board has provided treatment recommendation for more than 550 patients who have journeyed to Cleveland Clinic for definitive management of their spine tumors. We anticipate further growth in our leading-edge spine tumor program over the coming years.

Center for Neurofibromatosis

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 experts in the diagnosis and treatment of NF type I and type II, as well as other less common forms of NF.

Medical care is coordinated through a team of neurologists who thoroughly evaluate each patient and determine which of the other specialty physicians and services at Cleveland Clinic are necessary. Because of the large volume of patients cared for, the other medical and surgical services have extensive experience in treating the complications of NF. Our physicians keep the patient’s primary care physician abreast of developments with every visit, and often work with the primary care doctor to provide comprehensive lifelong principal care so that all the patient’s specialty care is at Cleveland Clinic.

Members of the medical team are world-renowned experts in the diagnosis and management of the pediatric brain tumors found in NF1, and have participated in and developed clinical trials involving new drug treatments for the brain tumors and plexiform neurofibromas that affect the lives of many patients.

Often, patients require brain or spinal surgery if tumors occur. Surgeons in our program have extensive experience in caring for these complications of NF. The surgeons in the Section of Skull Base Surgery focus on management of benign brain tumors often found in NF, including meningiomas and schwannomas. Surgeons in the BTNC and Spine Center have extensive experience in the surgical removal and spinal stabilization procedures often required by those with NF. Use of newly developed spinal radiosurgery techniques has provided a non-invasive method of treating select tumors.

Patients and their families can be assured that their needs will be cared for in a comprehensive, well-coordinated and compassionate fashion by physicians and nurses who are nationally recognized as leaders in the management of NF.

Section of Skull Base Surgery

As the surgical arm of the Center for Neurofibromatosis and Benign Tumors, the Section of Skull Base Surgery focuses on management of benign brain tumors (e.g., meningiomas and schwannomas) as well as skull base malignant tumors (sinonasal carcinomas, chordomas, chondrosarcomas).

Cleveland Clinic’s Skull Base Surgery Program within the BTNC is internationally recognized as one of the largest programs specializing in the management of meningiomas, evaluating more than 200 new meningioma patients annually. Among these, approximately 50 percent of patients are treated with surgery and 15 percent with Gamma Knife radiosurgery or conventional radiation.

In addition to its large clinical volume, the Section of Skull Base Surgery is one of the most productive programs internationally in the area of meningioma clinical research. More than 15 journal articles and book chapters were published in 2006 and 2007, with 23 additional publications in press in 2008.
Clinical Programs (continued)

In 2007, further expertise in endoscopic surgery for skull base indications was provided with the addition of Dr. Burak Sade to the Skull Base Surgery Program.

BTNC endoscopic neurosurgeons work closely with endoscopic sinus surgeons in Cleveland Clinic’s Head and Neck Institute to provide minimally invasive surgical management for skull base malignancies, in addition to pituitary region tumors.

Pituitary and Neuro-Endocrine Center (PNEC)

The Neuro-Endocrine Center has shown continuous growth since its inception in 2002, fostered by a close working relationship among members of the BTNC and the departments of Endocrinology, Diabetes and Metabolism; Neurological Surgery; Neuro-Ophthalmology; and Radiation Oncology. The close relationship has led to the development of highly integrated clinical care pathways, a common pituitary tumor research database and several joint research projects (see below).

Clinical Care Pathways

Clinical care pathways define the pre-hospital, periorative and postoperative care for patients with secretory and non-secretory pituitary tumors. The development of new pathways has helped decrease patient length of stay, with equal patient outcomes.

Academic Activities

A prospective IRB-approved database has been established for all patients with pituitary tumors seen in the Neuro-Endocrine Center. Detailed preoperative endocrine testing, including Cortrosyn stimulation, is routinely performed for comparison to postoperative findings. New clinical care pathways have eliminated the routine use of periorative steroids, thereby enabling the accurate determination of postoperative pituitary adrenal activity. Several retrospective analyses have been completed and are also in progress, including comparison of Gamma Knife vs. IMRT for subtotally resected somatotrophic pituitary adenomas, case review of pituicytoma, an analysis of the impact of somatostatin on the efficacy of radiosurgery for somatotrophic adenoma, and an evaluation of the role of radiosurgery and postoperative pituitary insufficiency. Additional collaborative work with groups outside Cleveland Clinic has focused on what role mutations in the aryl hydrocarbon receptor interacting protein gene (AIP) may play in the formation of pituitary tumors, especially familial acromegaly (excess growth hormone secretion due to a pituitary tumor) or in the early onset of these tumors in the sporadic setting. This resulted in two publications in 2007-2008: Georgitisi et al, Proceedings of the National Academy of Sciences USA (PNAS), 104(10): 4101-5, 2007 and Clinical Endocrinology, 2008, in press.

Teaching of residents and fellows has similarly been augmented through the establishment of the center. Endocrine residents routinely participate in outpatient evaluation with endocrinologists and surgeons. BTNC fellows are intimately involved in the outpatient, operative and inpatient care of all patients. Neurosurgery residents play a critical role in the inpatient and surgical care of these patients, and are frequently able to attend outpatient clinics. A joint conference involving endocrinology, neurosurgery, neuro-ophthalmology, neuroradiology and radiation oncology is held on the first Friday of each month, during which case presentations and management or visiting lecturers are presented.

In addition, monthly pathology review sessions, where the pathological findings of each patient are reviewed jointly by the pathologists, endocrinologists and neurosurgeons (the Pituitary Interest Group), continue. These sessions are open to all interested parties and are held the first Monday of the month in the Pathology & Laboratory Medicine Institute. A dedicated Advanced Neurosurgical and Spine Skills and Simulation Laboratory (ANSSSL) has also been developed through the Pituitary and Neuro-Endocrine Center’s
leadership, within the Department of Neurosurgery. A prime focus is the training of medical students and neurosurgery residents, as well as fellows and staff, in open, minimally invasive and endoscopic approaches to the brain and skull base, especially the anterior skull base via transnasal and para-sellar approaches.

Neuropathology

Neuropathologists Dr. Richard Prayson, Section Head, and Dr. Susan Staugaitis perform interoperative consultations and final pathologic diagnoses on more than 600 brain and pituitary tumor specimens each year. More than 450 of these specimens have been digitally captured for discussion at the BTNC patient management conferences. All glioma specimens are evaluated by a panel of ancillary immunohistochemical and molecular tests. The staff of the BTNC has indicated that the following panel is medically necessary because it provides additional information for prognosis and/or treatment planning:

**WHO Grade I Glioma**
- Ki-67 immunohistochemistry (proliferation index)

**WHO Grade II**
- Ki-67 immunohistochemistry (proliferation index)
- P53 immunohistochemistry (surrogate marker for p53 point mutation)
- Fluorescence in situ hybridization (FISH) for evaluation of allelic loss of chromosomes 1p and 19q
- (FISH for evaluation of Epidermal Growth Factor Receptor amplification is performed on WHO Grade II gliomas but billed to BTNC Research Account.)

**WHO Grade III-IV**
- Ki-67 immunohistochemistry (proliferation index)
- P53 immunohistochemistry (surrogate marker for p53 point mutation)
- Fluorescence in situ hybridization (FISH) for evaluation of allelic loss of chromosomes 1p and 19q
- FISH for evaluation of Epidermal Growth Factor Receptor amplification
- Analysis of 1p and 19q using LOH by PCR is performed on selected cases when this procedure provides more accurate or additional information.
- Due to low volume of request, sequencing of TP53 is no longer performed in house, but can be performed on a “send-out” basis.
- Testing of MGMT promoter methylation is also offered as a “send-out” test.

Approximately one-third of the 1p/19q FISH analyses performed are Reference Laboratory procedures (patients are not BTNC patients at the time of request).

Molecular Diagnostic Test Volume (Reporting Period 1/1/2008-12/31/2008)

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<th>Specimen Class</th>
<th>Total 1p FISH</th>
<th>Total 19q FISH</th>
<th>FISH for EGFR**</th>
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<th>19q LOH by PCR</th>
<th>TP53 SEQ</th>
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<tr>
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</tbody>
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* Specimen Classes SX and SO are patients treated by BTNC physicians.
** Numbers do not include tests performed on WHO Grade II gliomas billed to research accounts.
Clinical Programs (continued)

Neuropsychology

New to the BTNC is the integration of the neuropsychology program into the clinical brain tumor program. Spearheaded by Dr. Michael Parsons, primary brain tumor patients, as well as some others, undergo neuropsychological assessments before and after craniotomy for tumor resection. These assessments often reveal latent cognitive dysfunction that may impact recovery and functionality after surgery and throughout their disease management. Patients with any type of tumor who exhibit cognitive symptoms can also avail themselves of these assessments to improve their management and life quality issues.

Neuroradiology

The sections of Neuroradiology and Magnetic Resonance Imaging at Cleveland Clinic provide a wide array of diagnostic capabilities for routine imaging studies, as well as research projects, in support of the BTNC. During the last year, there has been a further interval increase in availability of high-field imaging within Cleveland Clinic hospitals and satellites. This enhances the capability of our patients and physicians to schedule MR imaging appointments at sites that are more convenient for the patients and more expeditious for patient management. All of these systems are managed centrally at Cleveland Clinic’s main campus, and the images are transmitted digitally so they are immediately available for comparison with prior studies on the central digital archive. Not only are the images immediately available to our diagnostic neuroradiology staff, but the finalized reports and digital images are also immediately available to our referring physicians through the electronic medical record. Images acquired at outside institutions have historically been problematic for Neuroradiology’s referring physicians. We recently piloted software in their clinics that enable the referring services to bypass the reviewing software on the outside CDs, review the outside images with a standardized program and upload the images onto Cleveland Clinic’s central archive for future reference if the patient is to be followed longitudinally by our physicians.

Diagnostic imaging capabilities in our system include routine imaging, diffusion imaging and high-resolution preoperative planning studies at all of our facilities. At our main campus, we also have the capability to provide MR perfusion imaging, diffusion tensor imaging, functional MRI and MR spectroscopy for more advanced preoperative planning. These data can now be fused with other DICOM data sets and incorporated into the stereotactic neurosurgical planning software.

The MRI facility is located immediately adjacent to the Gamma Knife Center, and has just completed reconstruction to better accommodate adult and pediatric sedation cases and to improve patient safety. Adult and pediatric anesthesiologists advance these efforts by routinely staffing the facility five days per week and providing continued emergency coverage after hours.

In addition, two new 3.0 Tesla whole-body MR machines have been installed in the hospital with upgraded gradient capabilities, a full complement of phased array coils, and a new 32-channel phased array head coil to enhance our inpatient capabilities in fast imaging, high-resolution imaging, 3D fast spin echo acquisitions and MR spectroscopy. These systems now allow us to perform preoperative diffusion tensor imaging and, shortly, functional MRI studies, which were previously available only in an outpatient facility at Cleveland Clinic’s Mellen Center for Multiple Sclerosis Treatment and Research.
Neuro-Oncology Nursing

Nurses, physician assistants and technicians specializing in the care of patients with brain tumors are an integral part of the BTNC. Members of the nursing and physician assistant team, which includes Cathy Brewer, Gail Ditz, Michele Gavin, Betty Jamison, Debra Kangisser, Kathy Lupica, Mary Miller, Carol Patton, Rachel Perez, Sherry Soeder, Laural Turo, Carla Duvall, Shelley Ogrin and Mary Murphy, are often the first contact for patients seeking an opinion or coming to the outpatient department for evaluation. The outpatient nursing team is overseen by Marcella Lupica.

Kathy Lupica facilitates our monthly Brain Tumor Support Group, which is attended by patients, families and friends. Ms. Lupica presented at several professional and patient conferences in 2008, including a lecture on “Brain Tumor Updates” at the Neuroscience Nursing Conference at Cleveland Clinic and “Brain Tumor Pathology Update” as part of a pre-conference workshop at the American Association of Neuroscience Nurses’ 40th Annual Educational Meeting in Nashville, Tennessee. She also co-presented “Brain Tumors: Facing the Challenge Together” for patients and loved ones, hosted at The Gathering Place.

Gail Ditz presented “Advances in Neuroimaging” as part of a preponderance workshop at the American Association of Neuroscience Nurses’ 40th Annual Educational Meeting. She also presented a lecture on “Neuroimaging for the Bedside Nurse” at the Neuroscience Nursing Conference at Cleveland Clinic.

Cathy Brewer and Carol Patton assist with patients interested in participating in or currently involved in research protocols. Betty Jamison works with patients undergoing Gamma Knife radiosurgery.

Nurse Practitioners
Kathy Lupica, Sherry Soeder, Carla Duvall and Shelley Ogrin

Nurse Clinicians
Gail Ditz, Betty Jamison, Rachel Perez, Laural Turo, Mary Miller, Mary Murphy

Research Nurses
Cathy Brewer, Carol Patton

Physician Assistants
Michele Gavin, Debra Kangisser
Clinical Research Programs/Innovations

Because many of the conditions we treat have no known cures, or the optimal treatment has not yet been defined, the BTNC is committed to the development of new and innovative treatments for patients with benign and malignant brain tumors. Our patients may elect to undergo experimental treatments or to participate in clinical research projects related to their diagnoses. Various chemotherapies and growth modifiers are among the experimental drug protocols developed by BTNC clinical investigators.

The BTNC was recognized in 2004 for its role as a leader in cutting-edge treatment and research by being selected as a full member of the prestigious New Approaches to Brain Tumor Therapy (NABTT) consortium. NABTT is one of only two national consortia funded by the National Cancer Institute to conduct Phase I and II trials of new treatments for brain tumors. This consortium has now merged with the North American Brain Tumor Consortium to form the Adult Brain Tumor Consortium (ABTC). The ABTC is the only consortium funded by the National Cancer Institute to conduct Phase I and II trials of new treatments for brain tumors.

The BTNC participated in several other consortia and cooperative groups, including Radiation Therapy Oncology Group (RTOG), Children’s Oncology Group (COG), American College of Surgeons Oncology Group (ACoSOG), International Blood Brain Barrier Consortium (IBBBDC) and South West Oncology Group (SWOG). Dr. Michael Vogelbaum is the Co-Chair of the Brain Tumor Committee and Chair of the Neurosurgery Committee for RTOG.

BTNC physicians also play leadership roles in other multicenter trials. Below are examples of single and multicenter clinical trials being led by BTNC physicians.

- **Phase II trial of patupilone in women with breast cancer brain metastases.** This multicenter trial tests a novel epothilone that crosses the blood-brain barrier. The study is headed by Dr. David Peereboom.

- **Phase II trial of ritonavir/opinavir in patients with progressive or recurrent high-grade gliomas.** This trial of an oral agent that inhibits tumor cell invasion was designed by Dr. David Peereboom.

- **Phase I/II trial of BMS-247550 for treatment of patients with recurrent high-grade gliomas.** This clinical trial examines an epothilone for patients with recurrent high-grade gliomas. Dr. David Peereboom is the PI for this national trial conducted within the NCI-sponsored NABTT CNS Consortium.

- **Phase III trial of radiation and/or chemotherapy for non-1p/19q codeleted anaplastic gliomas.** Dr. Michael Vogelbaum is the U.S. PI for this international effort being coordinated by the EORTC, a European cooperative trial group.

Additional clinical research programs include:

1. **Intra-arterial chemotherapy with blood-brain barrier disruption (BBBD) for primary central nervous system lymphoma (PCNSL) and other tumors** – Dr. Lilyana Angelov has developed a consortium-wide database for the tabulation of treatment results of this procedure for patients with PCNSL. This effort has produced a very large multicenter series regarding the treatment of newly diagnosed PCNSL patients with osmotic BBBD and intra-arterial chemotherapy – work that has been the subject of numerous peer-reviewed requested presentations and manuscript submissions. Further, the BTNC staff has contributed to the writing of several new protocols for the consortium as well as making several presentations at the consortium’s annual meetings. Several staff members have contributed to publication of the proceedings from this meeting, as well as other meetings on this topic.

2. **Erlotinib/temozolomide and postoperative radiation for newly diagnosed glioblastoma multiforme (GBM)** – Dr. David Peereboom led a Phase II trial of erlotinib with temozolomide and concurrent...
radiation therapy postoperatively in patients with newly diagnosed GBM. This single-institution trial completed accrual in 2007. This study was the first to combine erlotinib with standard therapy for patients with newly diagnosed glioblastomas. The manuscript has been submitted to the journal *Neuro-Oncology*.

3. **Intraoperative radiation therapy for solitary brain metastases** – Dr. Robert Weil is conducting a Phase I/II study utilizing a novel method for delivering intraoperative radiation therapy (INTRABEAM) for the treatment of a resected solitary brain metastasis. This method allows the precise delivery of radiation therapy directly into the tumor cavity and allows the patient with a solitary resectable brain metastasis to postpone the need for whole brain radiation.

4. **Convection-enhanced delivery (CED) of antitumoral agents** – This program uses the slow, continuous infusion of agents targeted to malignant glioma. This technique has the potential to deliver agents that otherwise cannot be delivered to the brain or that are too toxic to other organs for systemic delivery. BTNC neurosurgeons have been actively involved in several trials as well as development of new investigations. A multicenter Phase I trial of CED of IL13PE38QQR for newly diagnosed GBM was led by Dr. Michael Vogelbaum and the results were published in 2007. Dr. Vogelbaum has also been developing new drugs and devices for CED in the Center for Translational Therapeutics. He is coordinating an effort, along with Cleveland Clinic Innovations, to bring a novel CED catheter to the Food and Drug Administration in order to make it available for upcoming CED trials. Dr. Vogelbaum also serves as Founding President of the Society for CNS Interstitial Delivery of Therapeutics, the first international organization dedicated to research in this technique.

5. **Laser interstitial thermal therapy** – Dr. Gene Barnett is leading the first human trial of a new system aimed at thermally ablating brain tumors. A side-firing laser is placed stereotactically into a recurrent glioblastoma and the thermal damage is monitored by real-time MR thermometry. Preclinical testing was completed in 2007, and Dr. Barnett treated the first patient with this device in 2008.

6. **Brain metastases trials** – The Section of Metastatic Disease has several clinical trials. Dr. Robert Weil is Cleveland Clinic’s principal investigator on the Department of Defense Center of Excellence grant for the eradication of breast cancer brain metastasis. As part of the grant, he and Dr. David Peereboom have activated a study in which a breast cancer chemotherapy drug is given prior to a clinically indicated surgical resection of a breast cancer brain metastasis. The tumor sample is then assayed for drug concentration to assess entry into a patient’s tumor. Dr. Weil will also establish cell lines from the resected tissue. Two clinical trials of patupilone in brain metastases, one for breast cancer and one for non–small-cell lung cancer brain metastases, are actively accruing patients and have shown activity in these patients. The multicenter breast cancer study was developed by Dr. David Peereboom. Another multicenter trial developed by the BTNC involves the use of sunitinib with delayed whole brain radiation therapy for patients with one to three brain metastases who have received stereotactic radiosurgery. The BTNC is actively involved in RTOG trials for brain metastases as well. The BTNC is completing accrual on a Phase I/II study of the PEC intraoperative radiotherapy device for the treatment of a resected solitary brain metastasis, a novel method for the delivery of intraoperative radiotherapy.
Clinical Research Programs/Innovations (continued)

7. Complementary and alternative medicine – Dr. Glen Stevens has received NIH funding for the first BTNC trial of complementary and alternative medicine. His trial, “Phase II Randomized Evaluation of 5-Lipoxygenase Inhibition by Dietary and Herbal Complementary and Alternative Medicine Approach Compared to Standard Dietary Control as an Adjuvant Therapy in Newly Diagnosed Glioblastoma Multiforme,” seeks to minimize brain edema in patients with GBM.

8. National trials led by BTNC investigators – Two NABTT consortium trials were led and coordinated by Dr. David Peereboom: Phase I/II trial of ixabepilone in patients with recurrent high-grade gliomas and a Phase II trial of erlotinib and sorafenib in patients with recurrent high-grade gliomas. Dr. Michael Vogelbaum is the U.S. PI for a European-led Phase III trial of radiation and/or chemotherapy for 1p/19q non-codeleted anaplastic gliomas. He is also the U.S. co-PI for another Phase III trial of radiation and/or chemotherapy for 1p/19q codeleted anaplastic gliomas.

9. Tumor-treating fields – Dr. Robert Weil is the local principal investigator of this novel, noninvasive means of using applied electromagnetic fields in an effort to treat recurrent glioblastoma.

10. Stereotactic radiosurgery – The BTNC remains active in cooperative group studies. One study compares stereotactic radiosurgery alone vs. stereotactic radiosurgery and whole brain radiation in the management of brain metastases (RTOG 0574).

11. Primary CNS lymphoma – This study is assessing the addition of rituximab, methotrexate and temozolomide to the management of primary CNS lymphoma (RTOG 0227).

12. Brain metastases from non–small-cell lung cancer – The BTNC is actively enrolling patients in an RTOG study to assess the role of chemotherapy in the management of brain metastases from non–small-cell lung cancer. The agents being investigated are erlotinib and temozolomide (RTOG 0320).

13. Developing RTOG studies – Phase III study using memantine to prevent cognitive dysfunction from whole brain radiation (RTOG 0614). Phase III study to assess the role of Avastin in the management of glioblastoma multiforme (RTOG 0825, Dr. Michael Vogelbaum is the Neurosurgical Chair).

14. Other clinical research interests – Dr. John Suh is actively interested in studying the role of radiosensitizers in the treatment of brain tumors. He has been an international PI for these studies. Dr. Samuel Chao is interested in the diagnosis and management of radiation necrosis, a complication following radiation treatment. He is working on protocols and developing a database.
Basic Research Research at Cleveland Clinic continues to grow and prosper through recruitment of outstanding new staff, improvement and expansion of facilities, development of extensive infrastructure and support services, and enhancement of education programs. Central to the success of the BTNC is advancing the care of brain tumor patients through better understanding of the causes and mechanisms of tumor development. Basic science research efforts are focused on identifying the genetic, cellular and molecular biology of malignant and benign brain tumors; investigating the mechanism of tumor formation; and exploring new therapeutic developments for brain tumor treatments.

Below are examples of projects being conducted in the basic research labs.

- Development of immunotherapy for malignant glioma using vaccines formed by fusing tumor cells with dendritic cells (Dr. Gregory Plautz)
- Characterization of the tumor antigen profile of brain tumor stem cells to determine whether there are common glioma antigens, which would make it possible to develop a standardized glioma vaccine (Dr. Gregory Plautz)
- The ability of dendritic cell/tumor cell fusion vaccines and adoptive transfer of tumor-sensitized T cells to cure established brain tumors, being tested in mouse models as a prelude to future clinical trials (Dr. Gregory Plautz)
- Investigations into alterations in DNA repair mechanisms that may improve the chemo- and radio-sensitivity of malignant gliomas (Dr. Michael Vogelbaum)
- Examination of the role of NFkappaB and IL-8 in driving the invasion of malignant gliomas (Dr. Michael Vogelbaum and Dr. Baisakhi Raychaudhuri)
- Production of tumor-specific toxicity in malignant gliomas by modified small interfering RNA molecules (Dr. Michael Vogelbaum and Dr. Jose Valerio)
- Development of a novel assay for MGMT function (Dr. Michael Vogelbaum and Dr. Cliff Robinson)

BTNC Primary Laboratories

Center for Translational Therapeutics – Vogelbaum Laboratory

The BTNC’s Center for Translational Therapeutics, directed by Dr. Michael A. Vogelbaum, performs pre-clinical testing of the most promising anti-cancer agents that may be of use for treating malignant brain tumors. One goal of the Center for Translational Therapeutics is to accelerate the lengthy and expensive process of testing new drugs targeted against brain tumors and to safely move these drugs into clinical trials as quickly as possible for the benefit of patients.

Physicians, researchers and scientists involved in this center work with pharmaceutical companies and other medical institutions to identify, obtain and test new compounds. The center’s efforts, including an international search for all potential brain tumor-relevant therapies, have yielded several promising agents for testing. Testing of new agents involves evaluating the toxicity and efficacy of these compounds in the laboratory and in animals that have brain tumors. In addition, we are investigating the optimal route of delivery of these drugs.

Because many new therapeutic agents cannot penetrate the central nervous system, center researchers are exploring alternative delivery methods. In addition to investigating the efficacy of oral delivery, researchers evaluate the efficacy of the agents when delivered intracerebrally – directly into the brain – via a specialized neurosurgical technique called convection-enhanced delivery (CED). Furthermore, in collaboration with investigators in the Department of Biomedical Engineering of Lerner Research Institute (LRI), we are evaluating alternative formulations using nanotechnology, which may enhance distribution of potential therapeutics within the brain.

The center has started research projects with a number of pharmaceutical and biotechnology companies ranging in size from small startup firms to some of the largest
publicly traded companies. What these companies have in common are novel drugs that are close to or in clinical trial, and that are rationally designed to be effective against malignant gliomas given the molecular and genetic makeup of these tumors. These drugs are targeted against molecules such as EGFR, mTOR/Akt, STAT3 and Raf-1 kinase. Our first translational clinical trial is with Tarceva/OSI-774, a selective EGFR kinase inhibitor small-molecule drug. This Phase II trial showed an encouraging rate of tumor responses and disease stabilization. In combination with work done in our preclinical models, this clinical trial raised important questions regarding the ability of the drug to penetrate the blood-brain barrier. As a result of these observations, we launched a follow-up trial in which patients undergo a tumor biopsy while receiving the drug. By analyzing the effects of Tarceva on the tumor tissues, we will be able to determine whether response to this drug depends primarily upon its ability to reach its intended target in the tumor.

The center has also worked closely with other laboratories at Cleveland Clinic to help develop novel therapeutics that may have application for patients with malignant brain tumors. We have evaluated methods for improving immune response to gliomas (in collaboration with James Finke, PhD, of the Department of Immunology in LRI), understanding the role of NFkB in regulating glioma cell migration and exploring the use of a new drug that may sensitize gliomas to temozolomide (in collaboration with Stanton Gerson, MD, Director of the Case Comprehensive Cancer Center). Our efforts have included collaborations with investigators who have traditionally worked outside the field of malignant brain tumors, including Qing Wang, PhD (Department of Molecular Cardiology, LRI), with whom we are investigating the role of a newly defined tumor angiogenesis gene.

Weil Laboratory

Gliomas and Glioblastomas The Weil Laboratory continues its work in genomic and protein profiling of brain tumors. This is very time-consuming, laborious work – one tumor at a time – but it is rewarding in terms of gaining a richer and more nuanced understanding of how these tumors may develop, progress and respond to therapy, especially with respect to finding new targets.

Additional work continues on deciphering the internal genetic and protein differences of malignant gliomas, using a variety of molecular genetic and proteomic methods. This is a long-term project that will proceed over a number of years, gaining strength and nuance as more tissues are studied and variations accounted for.

For example, Khatri RG, Navaratne K, Weil RJ. “The Role of a Single Nucleotide Polymorphism of MDM2 in Glioblastoma.” Journal of Neurosurgery, November 2008, details how a single-nucleotide polymorphism (SNP), which is a normal variant in the DNA sequence encoding a protein, can lead to altered signaling of that or other proteins. In this case, the G allele is expressed more commonly in patients with glioblastoma multiforme (GBM), and this leads to higher levels of MDM2, irrespective of the levels of Tp53, which normally controls MDM2. Higher levels of MDM2, which acts as an oncogene (a tumor-promoting gene), are known to enhance tumor growth in many cancers, including GBM. This work suggests that a common SNP variant, which anyone may have, and which would not cause problems in the normal cell, may enhance cancer in those patients who develop a GBM.

Brain Metastasis Metastatic tumors to the brain, which occur in up to 200,000 people per year, represent a significant source of neurological debility and premature death, and are a second clinical and research focus of this laboratory effort.

Support from the Burkhardt Chair permitted preliminary work in proteomics of breast cancer metastasis that supported a successful grant application. Dr. Robert Weil is Cleveland Clinic’s principal investigator on a recently awarded Department of Defense Center of Excellence (COE) grant, five years in length and
involving approximately 10 centers, to study the process of CNS metastasis in breast cancer patients. Overall, it is a $17 million award (direct and indirect costs), with nearly $2.7 million coming to Cleveland Clinic to fund a clinical trial, the majority to fund proteomics research on the identification of proteins that go with the process of brain metastasis. Patricia Steeg, the head of the Women’s Cancers Section at the National Cancer Institute, is the lead Principal Investigator for the COE. Work on proteomic profiling, comparing breast cancers from women who have never developed a brain metastasis with those who have, is ongoing. The goal is to identify a set of genes and proteins in the original breast cancer that may suggest which women may be at risk of developing breast cancer that will metastasize to the brain, both to develop surveillance methods to find such tumors early and, more importantly, to devise strategies and treatments that may prevent them from developing.

Pituitary Tumors This is an area of clinical interest in which several important publications have resulted from work done together with Lauri Aaltonen in Finland, showing that mutations in the aryl hydrocarbon receptor interacting protein gene (AIP) may play a role in the formation of pituitary tumors, especially familial acromegaly (excess growth hormone secretion due to a pituitary tumor) or early onset of these tumors in the sporadic setting. This has resulted in two publications in prestigious journals, including *Proceedings of the National Academy of Sciences USA* (PNAS), 104(10): 4101-5, 2007 and *Clinical Endocrinology*, in press.

Collaborative Laboratories

*Jeremy Rich, MD, PhD*

Dr. Rich joined Cleveland Clinic as Chair of the Genomics Institute in September 2008. He is a world-renowned expert on brain tumor stem cells as well as being a clinical neuro-oncologist. Dr. Rich will carry on his cutting-edge brain tumor stem cell research in collaboration with BTNC clinicians and scientists.

*Jaharul Haque, PhD*

Dr. Haque’s laboratory investigates the role of the transcription factor STAT3 to drive the malignant behavior of gliomas. In collaboration with Dr. Michael Vogelbaum, this project obtained NIH funding: “Cytokine Signaling in Glioblastoma Cells.” NIH R01 CA 95006-01 (MAV co-PI; 10% effort; PI: Jaharul Haque PhD; 6/1/03 – 5/31/08, total direct costs: $1.6 million) and generated multiple peer-reviewed publications. A follow-up funding proposal has been submitted to NIH for review.

*Susan Brady-Kalnay, PhD*

Dr. Brady-Kalnay’s laboratory has investigated the role of a novel phosphatase in regulating the invasion and migration of malignant glioma cells. In collaboration with Dr. Michael Vogelbaum, this project obtained NIH funding: “PTPµ Suppresses Brain Tumor Cell Migration and Dispersal.” NIH R01 NS051520-01A1 (MAV collaborator, 5% effort; PI: Susan Brady-Kalnay PhD; 6/1/2006 – 5/31/2011, total direct costs: $1.9 million). Over the course of this granting period, we have performed in vivo studies to evaluate how alterations in the functioning of PTPµ affect the ability of human glioma xenografts to invade in rodent brains.

*James Finke, PhD*

Dr. Finke has been involved with investigation of the immunobiology of gliomas. Prior studies of malignant gliomas have shown that gliomas are immunosuppressive, as evidenced by decreased T cell function and the presence of apoptosis in a subset of lymphocytes from patients’ blood. GBMs are known to overexpress several different gangliosides that can be shed from the tumor and promote T cell dysfunction. More recently, it has also been clear that the tumor microenvironment can promote the accumulation of immune cells with suppressive activity that can prevent the development of anti-tumor immunity. This includes the T-regulatory population as well as myeloid derived suppressor cells (MDSC). Understanding

*Denotes Cleveland Clinic physician or scientist.*
the role that GBM-derived gangliosides, as well as immune suppressive cells, play in dampening the T cell response to this tumor is important – as is defining their mechanisms of action. We and others propose that effective immunotherapy will likely be achieved by combining either vaccine or adoptive T cell therapy with agents that can reduce the immune suppression.

To this end, we have been evaluating the immunosuppressive properties of gangliosides isolated from GBM cell lines. Previously, we reported that human gliolastoma cell lines and isolated gangliosides induce apoptosis in peripheral blood T cells. More recently, we examined the mechanism by which GBM lines and gangliosides induce apoptosis. Peripheral blood T cells activated with anti-CD3 (OKT3)/anti-CD28 antibodies were cultured either with GBM cell lines or with GBM cell line derived-gangliosides (10-20 mg/ml) for 48 to 72 hours prior to assessing apoptosis (nuclear blebbing detected by DAPI staining), caspase (-3,-8,-9) activation, and changes in the expression of the anti-apoptotic proteins Bcl-2 and RelA. When compared with T cells co-cultured with media alone, those co-cultured with all three GBM cell lines (CCF52, CCF4 and U87) showed apoptotic blebbing and reduced expression of RelA and Bcl-2 but not b-actin as a control protein. The reduction in the expression of the anti-apoptotic proteins likely contributes to the promotion of T cell death following exposure to GBM cell lines. Caspases, which are proteins critical for initiating the death sequence for apoptosis, were also activated in T cells by exposure to tumor cell lines, as demonstrated by the appearance of cleaved caspase-3 and -8 fragments and the reduction in caspase-9 proform.

That gangliosides derived from the GBM cells are important for induction of T cell death is supported by the demonstration that gangliosides derived from the GBM lines can mimic the apoptotic events induced by the RCC lines. Gangliosides isolated from the three GBM cell lines contained significant levels of GM2, GM1 and GD1a as determined by HPTLC and ELISA analysis. These GBM cell line-derived gangliosides induced RelA degradation along with T cell death in 72 hours. It was also demonstrated that exposure of T cells to GBM-derived gangliosides induced the formation of reactive oxygen species (ROS) within 12 to 18 hours, which was followed by mitochondrial damage. Western blotting demonstrated that gangliosides from all three cell lines induced mitochondrial damage as evident by the release of cytochrome-c into the cytosol. Additionally, mitochondrial permeability transition (MPT) was observed as detected by reduced uptake of the mitochondrial dye DiOC6 in T cells treated with the gangliosides compared with the untreated cells.

GBM-derived gangliosides also resulted in the activation of the effector caspase-3 along with both initiator caspas (-9 and -8). The addition of caspase-8 or -9 inhibitors to the cell cultures demonstrated that the caspase-8 inhibitor was more effective at protecting T cells from apoptosis (60 percent protection) than was the caspase-9 inhibitor (25 percent protection). Interestingly, both the caspase-8 and -9 inhibitors were equally effective at blocking caspase-8 and caspase-3 activation. These findings show that GBM-derived gangliosides induce T cell death by reducing the expression of key anti-apoptotic proteins (RelA and Bcl-2) and by inducing ROS formation mitochondrial damage along with caspase activation. This study also shows that caspase-8, which is typically associated with death receptor-mediated apoptosis (Fas, TNFα), is clearly critical for ganglioside-mediated apoptosis.

We have also started examining peripheral blood T cells from GBM patients for their staining with antibodies to gangliosides that are typically not detected on T cells from healthy donors, but are expressed by GBMs. This same kind of study has shown that the gangliosides GM2 and GD2 are detected on T cells from patients with renal cancer, but not normal donor T cells. The
GM2/GD2 positive cells are clearly more apoptotic than the GM2/GD2 negative T cells from the same patient. Whether we observe the same findings with T cells from GBM patients will be examined. As part of these studies, we will also test whether the peripheral blood from GBM patients contains a significant number of MDSC when compared with blood from healthy donors. Increased number of MDSC has been observed in peripheral blood of cancer patients, although there have been no studies in GBM patients. If MDSC are increased in number, we will assess that they suppress activity in vitro and if the tyrosine kinase inhibitor sunitinib can inhibit their suppressive activity or induce apoptosis in these cells.

**Stanton Gerson, MD, and Lili Liu, PhD**

Dr. Gerson and Dr. Liu are recognized authorities regarding the role of DNA repair enzymes in mediating resistance of tumor cells to chemotherapy. In collaboration with Dr. Michael Vogelbaum, they are evaluating the roles of the MGMT and base excision repair pathways in mediating the chemoresistance of gliomas. Multiple laboratory projects are ongoing and a funding proposal is being developed.

**Damir Janigro, PhD** *

Since 2007, the Center for Cerebrovascular Research, directed by Dr. Janigro, has been investigating proteomic markers for brain metastases in patients initially diagnosed with lung cancer. This study has been performed in conjunction with Dr. Peter Mazzone from the Department of Pulmonary Medicine and Dr. Tarek Mekhail from the Department of Hematology/Oncology, as well as Dr. Thomas Masaryk from the Section of Neuroradiology. The study initially centered on the well-known marker of blood-brain barrier integrity, S-100b but, like the CSF counterpart marker, transthyretin monomer (also known as prealbumin monomer), has been found to be falsely elevated by the presence of small vessel ischemic disease (SVID), which is most prevalent in the elderly and those with diabetes mellitus and/or hypertension.

A recent prospective study completed by medical resident Dr. J. Michael Taylor, performing research in Dr. Janigro’s lab and presenting at the ShowCASE 2008 conference at Case Western Reserve University, found that of more than 550 lung cancer cases followed at Cleveland Clinic over the past five years, the majority of these patients (358, or 65 percent) were found to have SVID by MRI. An auxiliary finding from the statistical analysis of these patients was that the presence of SVID appeared to correlate with a decreased incidence of brain metastases (14.0 percent) when compared with those who did not have findings of SVID by MRI (33.7 percent; \( P < 0.01 \)). Earlier work performed by Vincent Fazio, MS, based on Dr. Janigro’s collaboration with Drs. Mazzone and Mekhail, uncovered a lung cancer patient who on initial presentation was negative for brain metastases but, upon a secondary MRI performed 16 months later, presented with multiple brain metastases. Although this finding was unfortunate for the patient, the comparison of these two serum samples from the same patient helped to eliminate non-metastatic related variations between lung cancer patients with and without the development of brain metastases.

Further studies of serum from lung cancer patients presenting with or without brain metastases, and for which the presence of SVID by MRI was determined through collaboration with Dr. Masaryk from Neuroradiology, identified the protein Proapolipoprotein A1 as a marker of brain metastases that was not found to be elevated during the presence of SVID. This work was validated by two-dimensional Western blotting of this variant for Apolipoprotein A1 performed by Mr. Fazio over an expanded isoelectric range from pl 4.7-5.9. This work has recently been published in work by Nicola Marchi, PhD, et al., Cancer 2008;112:1313–24.

*Denotes Cleveland Clinic physician or scientist.
Established in 2001, Cleveland Clinic’s Brain Tumor and Neuro-Oncology Center (formerly Brain Tumor Institute) is among the leading programs in the United States for the diagnosis and treatment of primary and metastatic tumors of the brain, spine and nerves and their effects on the nervous system. Now part of the newly established Cleveland Clinic Neurological Institute, the Brain Tumor and Neuro-Oncology Center closely collaborates with Taussig Cancer Institute to provide innovative solutions for these complex problems, utilizing the latest technology.

Under the direction of Gene Barnett, MD; Michael Vogelbaum, MD, PhD, Associate Director; George Lawrence, Administrator; and Theresa Naska, Manager, success continued in 2008, with more patients than ever being served, and more than a quarter of new patients coming from outside Ohio. We expanded our services, improved patient satisfaction, attracted world-class physicians and scientists to our staff, made significant advances in basic and clinical research, and offered a broad array of educational experiences, including international forums.

The BTNC’s clinical research infrastructure is fully integrated with that of Cleveland Clinic Taussig Cancer Institute. All clinical protocols and correspondences, including IRB submissions (e.g., protocol amendments, safety reports), protocol budget creation, nursing assignment and study start-up, are funneled into the BTNC through Theresa Naska and processed through BTNC study coordinators Kathy Robinson and Marci Ciolfi. Material is dispersed from this central resource to all appropriate parties. The BTNC has two dedicated research nurses, Cathy Brewer and Carol Patton, who manage all clinical trials, including patient consent, monitoring and follow-up. These nurses are part of the Taussig Cancer Institute program and are backed up by other Taussig Cancer Institute research nurses. The program oversees and manages all regulatory matters, IRB submissions and all data collection/CRF transcription responsibilities through the dedicated BTNC study coordinators.

Cleveland Clinic Taussig Cancer Institute is affiliated with Case Western Reserve University and University Hospitals Case Medical Center. This relationship provides the opportunity to integrate an outstanding group of cancer researchers and a large cancer referral network as part of Northern Ohio’s only National Cancer Institute-designated Comprehensive Cancer Center based at Case.

The Case Comprehensive Cancer Center combines, under a single leadership structure, the cancer research activities of the largest biomedical research and health care institutions in Ohio – Case Western Reserve University, Cleveland Clinic and University Hospitals of Cleveland – into a unified cancer research center. With this integration, the Case Comprehensive Cancer Center has strengthened its scientific programs, expanded opportunities for disease-focused research, and enhanced access and ability to serve the entire population of Northeast Ohio.

The Cleveland community has fully embraced this exceptional opportunity to join the region’s two pre-eminent healthcare delivery systems and Case, their academic partner, into a single NCI-designated Comprehensive Cancer Center.
Program Development

Professional Recruitment

The addition of Dr. Jeremy Rich to Cleveland Clinic as Chairman of its Genomics Institute was a major coup for the institution and the BTNC. Dr. Rich is an internationally recognized expert in the field of brain tumor stem cells – both a potential cause as well as treatment for certain brain tumors. Dr. Rich, a neuro-oncologist, will be working closely with BTNC clinical and research staff in his pursuit of new insights and therapies for brain tumors.

The BTNC also participated in the successful recruitment of Dr. Candece Gladson. Dr. Gladson is a senior, funded scientist in brain tumor research. Dr. Gladson’s interests include molecular mechanisms involved in malignant astrocytoma cell migration, invasion and proliferation; cell adhesion receptors mechanisms; determining the signals generated by engagement of specific integrins and how these signals promote cell proliferation and migration; and brain tumor cell invasion, proliferation and their quantification. She joined the staff of Cleveland Clinic in January 2009.

The BTNC is actively recruiting an additional adult neuro-oncologist to help meet the clinical needs of our ever-increasing patient population.

Marketing/Advertising

Many marketing and advertising initiatives were implemented to create awareness of the BTNC in 2008. Because brain tumor patients are information savvy and seek out the latest in medical options for their condition, the BTNC website is a particularly important marketing tool. A primary focus in 2008 has been on redesigning the BTNC web pages and updating the content. The content will be strategically optimized to increase the natural rankings of the BTNC web pages on search engines.

Specific BTNC 2008 Marketing/Advertising Initiatives

National physician mailing – To increase geographic reach of physician referrals, a letter and fact sheet were mailed to potential referring physicians across the country. The mailing was executed in the fall, and success will be measured based on referral activity over the next six months.

Web banner advertising campaign – Developed to offer consumers access to BTNC patient informational webcasts on the following topics:

- **Advances in surgery for brain tumors**, Gene Barnett, MD
- **Intraoperative imaging for brain tumor surgery**, Gene Barnett, MD
- **Chemotherapy for brain tumors**, David Peereboom, MD

The campaign is aimed at drawing appointments from outside the local market. The current click-through rate is .08 percent compared with an industry average of .05 percent.

NI Publications

BTNC articles were featured in nearly all of the Neurological Institute publications, including Neuroscience Pathways, which is mailed to neurologists and neurosurgeons nationally and to primary care specialists regionally. The BTNC was featured in the following articles:

Spring 2008

- **T Cell Immunotherapy for Malignant Brain Tumors**, Gregory Plautz, MD
- A number of BTNC clinical trials

Fall 2008

- **Making the Inoperable Operable: Subcortical Navigation for Brain Tumors**, Gene Barnett, MD
- A number of BTNC clinical trials
The NI annual report, which is mailed to a similar audience as *Neuroscience Pathways*, prominently featured the BTNC, with presence in the following areas:

- Clinical Programs
- Neuro-Oncology
- Neurosurgical Oncology and Radiation Neuro-Oncology
- Fellowships
- Clinical Research
- Laboratory Research
- Outcomes
- Patient Success Story – Joe Case
- CME Courses

The BTNC was also featured in the spring 2008 issue of *Spinal Column*, which is mailed to neurologists, neurosurgeons, chiropractors, orthopaedic surgeons, rheumatologists and sports medicine, family practice, internal medicine and geriatric physicians in Ohio and six contiguous states. The BTNC was featured in the following article:

- Stereotactic Spine Radiosurgery, Lilyana Angelov, MD

**Other Publications**

**Taussig Cancer Institute publications** – Spring edition of *Cancer Consult* included a number of BTNC clinical trials and the fall edition included the following:

- *Making the Inoperable Operable: Subcortical Navigation for Brain Tumors*, Gene Barnett, MD
- *T Cell Immunotherapy for Malignant Brain Tumors*, Gregory Plautz, MD
- A number of BTNC clinical trials

**BTNC clinical trials mailer** – Mailer sent to neurologists, neurosurgeons, oncologists, hematologists, and family practice and internal medicine physicians in Ohio and six contiguous states in early October 2008 that included the following trials:

- Celldex (RT/Temozolomide) IRB CC311
- RTOG 0277 Methotrexate, Rituximab, Temodar IRB CC238
- CCF IRB CC526 MONT 1307

**Website enhancements** – Currently working on redesigning the layout of the BTNC website and updating content.

**Other**

- ABTA – Display at patient conference
- ASCO display – BTNC informational materials were offered as handouts
- VirtualTrials.org – Website sponsorship and banner ad placement
- Pituitary.org – Hospital membership and physician membership for Dr. Robert Weil
- Gamma Knife umbrellas – New Gamma Knife golf umbrellas ordered for the Gamma Knife training session in late 2008

**BTNC in the News**

**Print**


*Plain Dealer, The Times-Picayune* – Two Cleveland hospitals are embarking on an experimental procedure using laser heat to “cook” brain tumors, offering hope of improved survival of one of the most difficult-to-treat cancers. 9/25/2008, 10/11/2008
**Outreach**

**International Outreach Services**

BTNC physicians work closely with neurosurgeons in Cleveland Clinic Florida to provide services for patients. Out-of-state patients can take advantage of Cleveland Clinic’s Medical Concierge program, a complimentary service that offers facilitation and coordination of multiple medical appointments; access to discounts on airline tickets and hotels, when available; help in making hotel reservations or housing accommodations; and arrangement of leisure activities.

BTNC and Gamma Knife Center specialists also treat patients from outside the United States. The special requirements of international patients are handled through Cleveland Clinic’s Global Patient Services program. The professionals within Global Patient Services provide the assistance and services our international patients need to help them feel at home while they are being treated here. We employ a large multilingual staff, and interpreters are available to assist patients. Our staff helps coordinate all the details of a visit, from scheduling medical appointments and making hotel and transportation arrangements to transferring and translating medical records.
Education

Continuing Medical Education/Professional Education

Supporting Professional Education As part of our mission to advance brain tumor treatment and research through collaboration and education, the BTNC and the Department of Neurosurgery coordinated and hosted two major symposia in 2008, including the Second International Symposium on Stereotactic Body Radiation Therapy and Stereotactic Radiosurgery, held in February in Orlando, Florida. The symposium featured national and international leaders in brain-, spine- and body-targeted stereotactic radiation modalities and techniques. This successful event brought together more than 150 participants who spent three days discussing advances in the treatment of benign and malignant tumors involving multiple organ sites. The BTNC also hosted a dual symposium in Cleveland on pituitary disease management for physicians and for patients in April, attracting more than 125 participants. In November, the BTNC was a joint sponsor with Mexican neurosurgical and neuro-oncology societies in Los Cabos, Mexico.

The BTNC's Gamma Knife Center, under the direction of Dr. John Suh, continues to be a major thrust for the BTNC. To support education, Cleveland Clinic had four hands-on Gamma Knife radiosurgery training courses for more than 30 people through December 2008.

Supporting Patient Education

The BTNC was a proud sponsor of the American Brain Tumor Association’s (ABTA) regional patient meeting in May 2008 in Chicago. Patients and their family members, healthcare providers and volunteers gathered to learn about various topics, from the biology of brain tumors to choosing between standard therapy and a clinical trial. Kathy Lupica, MSN, CNP, and Mary Murphy, RN, BSN, as well as Marketing Manager Colleen Burke, made information available to patients. Kathy Lupica also presented a concurrent workshop to patients titled “The Caregiver Journey.” A monthly brain tumor support group for patients, families and friends is facilitated by Kathy Lupica.

Fellowships

The BTNC has two neurosurgical oncology fellowship programs. One is a two-year, combined clinical and laboratory research fellowship program, which provides exposure to the design and operation of clinical trials as well as opportunities to contribute to the neuro-oncology literature. Fellows are expected to participate in the design, IRB application process and management of new clinical trials during this fellowship, and to produce clinical presentations and reports.

The second fellowship is run by the Section of Skull Base Surgery. By combining the highly specialized techniques of interventional neuroradiology, otolaryngology, neurosurgery, ophthalmology and plastic surgery, the principal goal of skull base surgery is to access deep-seated, difficult-to-reach lesions by anatomic displacement or extensive removal of the base of the skull. These techniques reduce or eliminate the need for brain retraction, thereby minimizing injury to the brain, cranial nerves and blood vessels.

Skull base surgery techniques are commonly used to treat various lesions in or around the paranasal sinuses and the floor of the anterior fossa, orbit, infratemporal fossa, sella, clivus, cavernous sinus, temporal bone/petrous apex, posterior fossa and the foramen magnum region.
Fellows, 2002 – Present

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# Appendix A – Clinical Trials (Adult)

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<td>3669</td>
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<td>Protocol A: Combination Chemotherapy (Methotrexate, Procarbazine, &amp; CCNU), Intraventricular Cytarabine &amp; Methotrexate, +/- Intra-Ocular Chemotherapy for Patients with Primary Central Nervous System Lymphoma (PCNSL) &amp; Protocol B: Combination Chemotherapy (Methotrexate, Cyclophosphamide &amp; Etoposide Phosphate) Delivered in Conjunction with Osmotic Blood-Brain Barrier Disruption (BBBD), with Intraventricular Cytarabine +/- Intra-Ocular Chemotherapy, in Patients with Primary Central Nervous System Lymphoma (PCNSL)</td>
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<td>NCTCTG RTOG 0574: 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>CC185</td>
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<td>Phase II Trial of Pazopanib in Patients with Brain Metastases from Breast Cancer</td>
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<td>CC190</td>
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<td>Phase I and II, Open-Label Multi-Center Trials of Pazopanib in Combination with Lapatinib in Adult Patients with Relapsed Malignant Glioma (Phase II)</td>
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<td>CC222</td>
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<td>A Feasibility Assessment and a Phase II Trial of MLN518 for Treatment of Patients with Recurrent Glioblastoma</td>
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<td>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>CC258</td>
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<td>NABTT 2201 PHASE II Study of ANTI-CD-20 Monoclonal Antibody (Rituximab) Therapy for Patients with Refractory or Relapsed Primary Central Nervous System Lymphoma (PCNSL)</td>
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<td>Phase Ib/IIa, Multicenter, Open-label Study of AQ4N in Combination with Radiation Therapy and Temozolomide, to Evaluate the Safety, Tolerability, and Efficacy in Subjects with Newly Diagnosed Glioblastoma Multiforme</td>
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<td>CC396 NOVA 1507</td>
<td>An Open-label, Multicenter, Phase II Study to Evaluate the Activity of Patepiline (EP0906), in the Treatment of Recurrent or Progressive Brain Metastases in Patients with NSCLC</td>
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<td>Phase I/II of Hydroxychloroquine in Conjunction w/RT</td>
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<td>Phase II Study of R-(−)-gossypol (Ascenta's AF-101) in Recurrent Glioblastoma Multiforme</td>
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<td>CC492 CASE 2307</td>
<td>Phase II Trial of Ritonavir/Lupinavir in Patients with Progressive or Recurrent High-Grade Gliomas</td>
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<td>NVCA 1306</td>
<td>Phase II Study for Patients with Relapsed Primary Central Nervous System Lymphoma</td>
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<td>Phase II Clinical Trial of Patients with High-Grade Glioma Treated with Intra-arterial Carboplatin-based Chemotherapy, Randomized to Treatment with or without Delayed Intravenous Sodium Thiosulfate as a Potential Chemoprotectant against Severe Thrombocytopenia</td>
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<td>Phase II Randomized Evaluation of Selective, S-Lipoxygenase Inhibition by Boswellia serrata Herbal Medicine Approach Compared to Control as an Adjuvant Therapy in Newly Diagnosed and Recurrent High Grade Gliomas; NIH Grant No. R21 CA107277-01</td>
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<td>Phase II Evaluation of a Stress Reduction Program in Patients with Malignant Brain Tumors and Their Family Caregivers</td>
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<td>Lived Experience of a Long Term Survivor with a Highly Malignant Brain Tumor</td>
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<td>4106</td>
<td>RTOG</td>
<td>Phase III Comparison of Biafine (r) to Declared Institutional Preference for Radiation Induced Skin Toxicity in Patients Undergoing Radiation Therapy for Advanced Squamous Cell Carcinomas of the Head and Neck (RTOG 99-13)</td>
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<td>A Phase 3 Randomized, Open-label Comparative Study of Standard Whole Brain Radiation Therapy with Supplemental Oxygen, with or without Concurrent RSR13 (efaproxiral), in Women with Brain Metastases from Breast Cancer</td>
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<td>7791</td>
<td>RTOG</td>
<td>RT0G G320; 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>Prospective Analysis of Wellness Following Gamma Knife for Non-Malignant Indications</td>
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<td>Phase III Trial of Motexafin Gadolinium with Whole Brain Radiation Therapy Followed by Stereotactic Radiosurgery Boost in the Treatment of Patients with Brain Metastases</td>
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<td>Prospective Study on the Short-term Adverse Effects from Gamma Knife Radiosurgery</td>
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<td>Phase III Study of Temozolomide-Based Chemotherapy Regimen for High Risk Low-Grade Gliomas</td>
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<td>RT0G G525; Phase III Trial Comparing Conventional Adjuvant Temozolomide with Dose-Intensive Temozolomide in Patients with Newly Diagnosed Glioblastoma</td>
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<td>CC238</td>
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<td>Phase II 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>CC559</td>
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<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>4369</td>
<td>NABTT</td>
<td>Phase I Gliadel and Escalating Doses of Intravenous O6-Benzylguanine Trial in Patients with Recurrent Malignant Gliomas</td>
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<td>Phase III Randomized Trial of the Role of Whole Brain Radiation Therapy in Addition to Radiosurgery in the Management of Patients with One to Three Metastases</td>
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<td>Phase II Trial of Tarceva In Patients with Recurrent / Progressive Glioblastoma Multiforme</td>
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### Appendix A – Clinical Trials (Adult) (continued)

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<td>Phase I Study of Convection Enhanced Delivery (CED) of IL13-PE38QQR Infusion after Resection Followed by Radiation Therapy with or without Temozolomide in Patients with New Diagnosed Supratentorial Malignant Glioma</td>
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<td>CC311 CLDX 1307</td>
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<td>Phase II/Ill Randomized Study of CDX-110 with Radiation &amp; Temozolomide in Patients with Newly Diagnosed GBM</td>
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<td>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>MGI 1307</td>
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<td>Phase II, Multicenter, Exploratory Study, Evaluating the Treatment of Surgery Plus GLIADEL Wafer in Patients with Metastatic Brain Cancer</td>
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<td>7003</td>
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<td>Phase III Study Utilizing the PEC Intraoperative Radiotherapy Device for the Treatment of a Resected Solitary Brain Metastasis</td>
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<td>CC126</td>
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<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>CC385 CASE 4107</td>
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<td>Clinical Study to Assess Entry of Chemotherapeutic Agents into Brain Metastases in Women with Breast Cancer</td>
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### Pediatric Trials: COG (Children’s Oncology Group)

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<td>ACNS0232</td>
<td>Radiotherapy vs. Chemotherapy in CNS Germinoma</td>
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<td>ACNS0331</td>
<td>RT and Chemotherapy in Medulloblastoma</td>
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<td>ACNS0423</td>
<td>Phase II Rx Radiation and Temozolomide and Temozolomide and CCNU in High Grade Gliomas</td>
<td>Tekautz T; Wiersma S</td>
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<td>ACNS0334</td>
<td>Phase III Randomized Trial for the Treatment of Newly Diagnosed Supratentorial PNET and High Risk Medulloblastoma in Children &lt;36 months old with Intensive Induction Chemotherapy with Methotrexate followed by Consolidation with Stem Cell Rescue vs. the Same Therapy without Methotrexate</td>
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<td>ANBL0531</td>
<td>Response and Biology-Based Therapy for Intermediate-risk Neuroblastoma</td>
<td>Tekautz T; Wiersma S</td>
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<td>ANBL0421</td>
<td>Irinotecan + Temozolomide in Neuroblastoma</td>
<td>Wiersma S; Tekautz T</td>
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<td>ACNS0121</td>
<td>Conformal RT Treatment for Ependymoma</td>
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<td>ACNS0122</td>
<td>Neoadjuvant Chemotherapy Chemo +/- Surgery for NGGCT</td>
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<td>ACNS0223</td>
<td>Carboplatin, Vincristine and Temozolomide in Gliomas</td>
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<td>ACNS0221</td>
<td>Conformal RT in Gliomas</td>
<td>Wiersma S; Hilden J, Burke M</td>
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<td>ACNS0222</td>
<td>Phase II Study of Motexafin-Gadolinium (NSC559238, IND #55583) and Involved Field Radiation Therapy for Intrinsic Pontine Glioma of Childhood</td>
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<tr>
<td>ACNS0332</td>
<td>Efficacy of Carboplatin Administered Concomitantly with Radiation and Isotretinoin as Pro-Apoptotic Agent in Other Than Average Risk Medulloblastoma/PNET Patients</td>
<td>Wiersma S; Tekautz T</td>
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Appendix B – Publications

Journal Publications


Appendix B - Publications (continued)


Appendix B - Publications (continued)


Book Chapters


Appendix C – Charts and Statistics

The Brain Tumor and Neuro-Oncology Center (BTNC) continues to grow in volume of procedures. 401 stereotactic radiosurgery (Gamma Knife and Novalis) and 573 surgical procedures were performed in 2008, which is a combined 62 percent increase compared with 2001.

Total outpatient visits increased by 366 percent over the past eight years. New patient visits have more than doubled since 2001.
The Neurological Institute is one of 26 institutes at Cleveland Clinic that group multiple specialties together to provide collaborative, patient-centered care. The institute is a leader in treating the most complex neurological disorders, advancing innovations such as deep brain stimulation, epilepsy surgery, stereotactic spine radiosurgery and blood-brain barrier disruption. Annually, our staff of more than 220 specialists serves 140,000 patients and performs 7,500 surgeries. Cleveland Clinic is a nonprofit multispecialty academic medical center, consistently ranked among the top hospitals in America by *U.S. News & World Report*. Founded in 1921, it is dedicated to providing quality specialized care and includes an outpatient clinic, a hospital with more than 1,000 staffed beds, an education institute and a research institute.