NewYork–Presbyterian

Neuroscience

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Spring 2004

Gamma Knife Expands Treatment Options

During the past decade, Gamma Knife radiosurgery has made possible a considerable number of advances in the field of neurosurgery. Researchers at NewYork-Presbyterian Hospital and its affiliated medical schools—Columbia University College of Physicians & Surgeons and Weill Medical College of Cornell University—continue to be at the forefront of the trend, applying this targeted modality to an ever-widening range of indications. Gamma Knife complements other radiosurgical options available through the Hospital, which has one of the most comprehensive radiosurgical programs in the country.

"Since our first radiosurgical treatment in 1989, we have continuously expanded our technology and experience," said Steven Isaacson, MD. "The goal is to improve the health of our patients and the well-being of their families."

Gamma Knife surgery is a safe and noninvasive modality. It is capable of delivering up to 201 beams of gamma radiation, which converge, with pinpoint accuracy, on the targeted abnormality in the brain. Because of the convergence of the rays, enough radiation is provided to treat the diseased area, yet the low intensity of each individual beam ensures the safety of surrounding healthy tissue.

Treatment with the Gamma Knife greatly reduces the incidence of complications after treatment in comparison with conventional therapy, and

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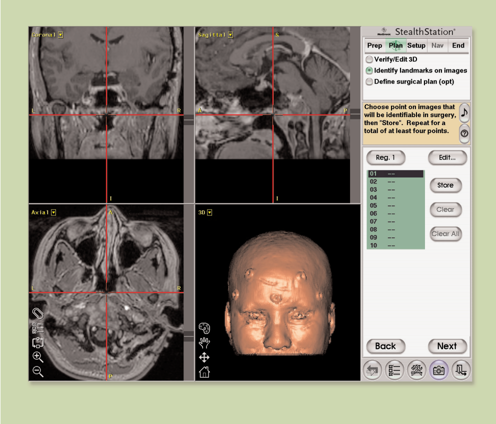
Personalizing Patient Care In Skull Base Surgery

Physicians at NewYork-Presbyterian Hospital and its affiliated medical schools—Columbia University College of Physicians & Surgeons and Weill Medical College of Cornell University—have developed an approach to skull base surgery that allows personalized attention to the disease process and the emotional aspects of patient care.



Navigation technologies allow neurosurgeons to navigate with precision.

"Skull base tumors are notorious for invading into multiple anatomical compartments, including the skull, brain, nasal sinuses, orbit, and neck," said Jeffrey N. Bruce, MD. "Our ability to draw on the expertise of a diverse group of surgeons, a multidisciplinary skull base team, enables us to handle even the most complex problems."

With a team of world-renowned experts striving to improve patient outcomes, the Hospital's program offers state-of-the-art treatment for a wide variety of tumors and vascular abnormalities, including acoustic neuromas, pituitary adenomas, chordomas, and carcinomas of the head and neck.

"There is nothing we can't handle," said Philip E. Stieg, PhD, MD.

Intensive microsurgery is frequently used to treat the skull base lesion. However, according to Susan Pannullo, MD, radiosurgical options may be the best modality for addressing a particular patient's pathology. That is why the treatment algorithm is developed based on the specific needs of each patient.

"We can choose from a variety of approaches," Dr. Pannullo said. "Physicians may be less comfortable treating with radiosurgery if their hospital doesn't have this great treatment option and a team to design the best way for treating that patient."

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- Brain Attack and Cerebrovascular Disease Update 2004—November 19th

NewYork-Presbyterian
The University Hospitals of Columbia and Cornell

NewYork-Presbyterian Neuroscience

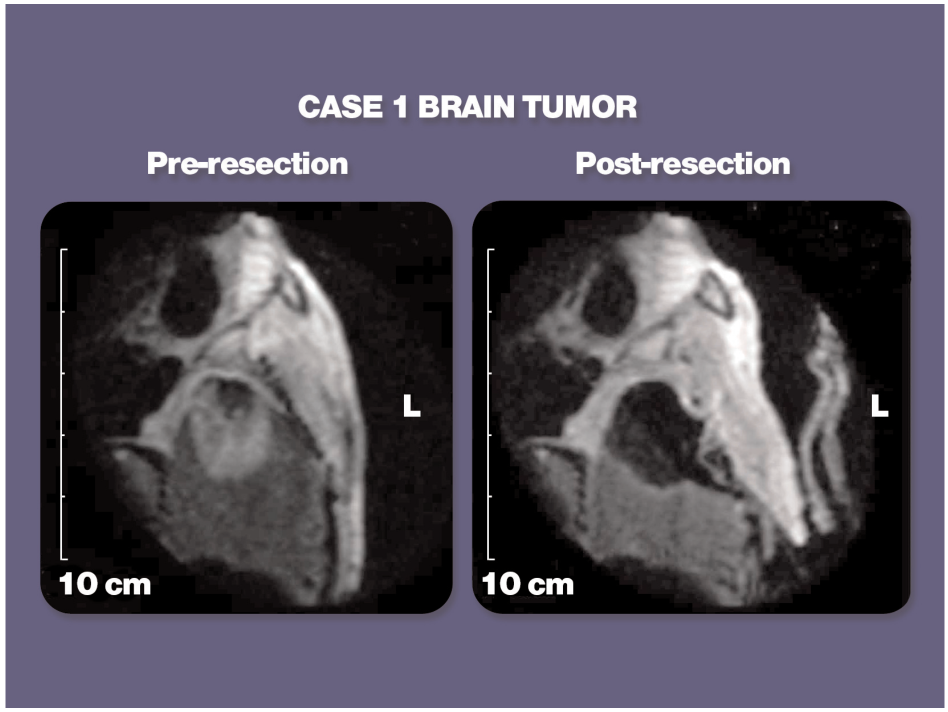
Expanding the Range of Image-Guided Neurosurgery

Using information-rich images of the brain obtained during surgery, neurosurgeons at NewYork-Presbyterian Hospital and Weill Medical College of Cornell University can perform sophisticated procedures with unprecedented precision. Called intraoperative magnetic resonance imaging, this process enables surgeons to visualize intracerebral lesions in real time, facilitating their complete resection and improving outcome.

"With intraoperative magnetic resonance imaging, we can acquire images in the operating room while we are working and adjust our surgical plan based on the updated information," said Theodore Schwartz, MD.

According to Dr. Schwartz, intraoperative magnetic resonance imaging allows the fullest possible resection of many brain tumors with maximum safety. It is also an option in cases of intractable epilepsy. The Department of Neurosurgery at NewYork-Presbyterian/ Weill Cornell owns 1 of just 17 units currently available in the United States.

Determining tumor margins and delineating brain structures precisely is always a challenge, and neurosurgeons have employed a variety of ingenious technologies over the years, ranging from computed tomography to conventional magnetic resonance imaging, to visualize the brain before surgery.



A left temporal brain tumor before and after resection. The image on the right displays a complete resection of the enhancing portion of the tumor, which was removed with the patient awake to preserve his language abilities.

During procedures, they have used the operating microscope and computer-assisted surgical navigation. All such systems are limited, however, because functional brain structures may shift slightly during surgery (though stereotactic methods can be used to develop accurate spatial coordinates and localize brain regions with a fair degree of precision).

One consequence of even minor alterations in the position of the brain parenchyma is that in the interest of avoiding harm to the patient, surgeons may perform resections that fail to include some portion of the lesion. A growing body of evidence indicates that incomplete resections are responsible for less-than-optimal results in about one third of cases in which only preoperative images are used. Fluoroscopy and computed tomography, other methods that can be used intraoperatively, in principle, lack the resolution of magnetic resonance imaging and have the practical disadvantage of exposing patients to ionizing radiation.

Developed in the mid-1990s and first reported in 1997, intraoperative magnetic resonance imaging was designed

> *"With intraoperative magnetic resonance imaging, we can acquire images in the operating room while we are working and adjust our surgical plan...."*
>
> *—Theodore Schwartz, MD*

in an attempt to address this problem. Because intraoperative magnetic resonance imaging works by analyzing radio waves, a mobile radio frequency shield is placed around the patient's head. The magnet of the scanner is weak enough that it does not affect the use of instruments.

Once an image is acquired, noted Dr. Schwartz, "we can use that information for what we call 'intraoperative navigation'—that is, we can point anywhere in the brain, and the computer will tell us exactly where we're pointing, from the intraoperative magnetic resonance imaging scan that we just took."

With its capacity to visualize tumor margins, intraoperative magnetic resonance imaging has been applied with great success in resecting various types of primary brain tumors, including lower-grade, slowly growing gliomas and higher-grade gliomas, which grow faster and are more often malignant. Transsphenoidal surgery for pituitary adenomas (benign neoplasms of the pituitary gland, which can be removed through the nose) is also greatly enhanced with the use of intraoperative magnetic resonance imaging.

In a recently published study (*Epilepsia* 2002;43:430-436), Dr. Schwartz and other researchers found that intraoperative magnetic resonance imaging appears to be useful in cases that call for a radical amygdalohippocampectomy. In this procedure, used to treat intractable medial temporal lobe epilepsy, surgeons remove the amygdala, hippocampus, and parahippocampal gyrus. Retrospective imaging studies indicate a higher rate of postoperative seizures if any portion of these structures escapes resection. Dr. Schwartz and colleagues followed 5 consecutive patients who underwent this procedure with the use of intraoperative magnetic resonance imaging and demonstrated postoperatively that the hippocampectomy was complete in all cases. These patients have remained seizure-free.

"We're doing the same operations we always did," said Dr. Schwartz. "We're just doing them better."

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NewYork-Presbyterian Neuroscience is a publication of the Neuroscience Centers of NewYork-Presbyterian Hospital. The Neuroscience Centers are at the forefront of research and practice in the diagnosis, treatment, and rehabilitation of neurologic disease. NewYork-Presbyterian Hospital is located at Columbia University Medical Center and NewYork Weill Cornell Medical Center. The Neuroscience Centers include the Neurological Institute at NewYork-Presbyterian Hospital/Columbia University Medical Center and the Weill Cornell Neuroscience Institute at NewYork-Presbyterian Hospital/Weill Cornell Medical Center, which are respectively affiliated with Columbia University College of Physicians & Surgeons and the Weill Medical College of Cornell University.

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Attacking Brain Tumors Directly

Can brain tumors defend themselves against a direct attack as well as they do against systemic (ie, intravenous) drug delivery? Researchers at the Herbert Irving Comprehensive Cancer Center at NewYork-Presbyterian Hospital/ Columbia University Medical Center are seeking to learn just that as part of an ongoing Phase I clinical trial.

"It's called convection-enhanced delivery," said Jeffrey Bruce, MD. "We stereotactically place 2 catheters around the tumor while the patient is under local anesthesia. The catheters emerge through the patient's scalp and are connected to an infusion pump at the bedside."

> "Convection-enhanced delivery avoids one of the key disadvantages of traditional chemotherapy, which is the need to cross the blood-brain barrier."
>
> —Jeffrey N. Bruce, MD

According to Dr. Bruce, the pump delivers a drug called topotecan directly into the tumor. This idea of direct drug delivery is not new; leaders in the field trace its development back to research at the National Institutes of Health (NIH) in the early 1990s.

"The procedure made a lot of sense to us, so we've been studying it in lab animals here for about 8 years," noted Dr. Bruce, adding that results from the animal studies led to the choice of topotecan as the therapeutic drug. "We tested about 30 antitumor drugs in the lab, and it worked the best," he continued.

In addition to the choice of drug agent, Dr. Bruce and his team believe that the key to potential success for convection-enhanced therapy is that it is delivered in a relatively low dosage via extremely slow microinfusion. "Patients remain attached to this pump for 4 days while just a few drops per hour are delivered into their tumor and surrounding brain," explained Dr. Bruce. He estimates the total dosage to be approximately 10 mL per day. This method aims to avoid the destructive side effects of the larger doses of chemotherapy required in systemic delivery.

Convection-enhanced therapy may be more viable in treating brain tumors than in treating some other cancers. According to Dr. Bruce, one "advantage" of brain tumors is that unlike breast cancer, for example, they do not metastasize to other organ systems. Thus, if the tumor can be attacked directly and contained, the prognosis is much brighter. In the laboratory tests conducted at NewYork-Presbyterian/Columbia, the animals were actually cured after therapy.

"Convection-enhanced delivery avoids one of the key disadvantages of traditional chemotherapy, which is the need to cross the blood–brain barrier. These blood vessels are designed to protect the brain against outside substances, like poisons," said. Dr. Bruce, adding that, obviously, chemotherapy is toxic. "That barrier is a key reason why traditional therapy needs a relatively high—and more virulent—dose of chemotherapeutic agent; it's the only way that any viable amount of drug will actually reach the tumor. However, with convection-enhanced delivery, you're already on the other side of the barrier."

That means two things, according to Dr. Bruce: 1) lower chemotherapy dosage from the outset (he estimates maybe 1/100th or even 1/1,000th of the traditional dose) and 2) what little drug there is does not cross back easily into the system (or have much effect if it does). Therefore, with a smaller amount, more drug is actually conveyed into the area that needs it, he explained.

Given the potential benefits of convection-enhanced delivery, one may wonder why tests did not begin sooner. NIH funding for the NewYork-Presbyterian/Columbia trial was finalized at the end of last year, and Dr. Bruce is accepting candidates. For the initial trial, he is seeking approximately 50 patients. "They should be young and otherwise healthy," he said. "Their tumor must be less than 100 mL in volume and recurrent. The treatment seems somewhat counterintuitive. The patient already has a mass in the brain, so presumably you wouldn't want to infuse anything and potentially swell the brain further. But that's not what happens in this therapy. The drug is infused so slowly and in such a relatively small dose that there is no problem with swelling."

Another potential objection, he continued, is that "one might think the drug wouldn't spread well with this method, since the brain is made of solid tissue, but it does."

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> *"We have neurosurgeons, radiation oncologists, clinical neuropsychologists, diagnostic neuroradiologists... [The hospital provides] an unprecedented level of service."*
>
> *— Steven Isaacson, MD*

The emotional aspects of treatment are addressed by support personnel, including a team of nurse practitioners, physician assistants and administrative staff. "We don't just view the patient as having a disease process we can treat surgically," said Dr. Stieg. "Because skull base surgeries are often extremely complex and difficult, time must be taken to explain the diagnosis, treatment options, and risks."

At NewYork-Presbyterian Hospital, neurological surgeons, otorhinolaryngologists, plastic surgeons, vascular surgeons, interventional neuroradiologists, and pediatric surgeons work in close collaboration with the patient to develop multimodal approaches for improving patient survival and quality of life. Surgeons have incorporated unique surgical approaches. For example, pituitary adenomas can be treated endoscopically in conjunction with intraoperative magnetic resonance imaging. This minimally invasive procedure eliminates the need for postoperative packing. Early results suggest the procedure shortens hospitalization time and achieves equivalent resections compared with an open procedure. "Intraoperative magnetic resonance imaging allows us to confirm complete removal of the tumor, while the endoscope allows us to do the procedure in a minimally invasive fashion," said Dr. Stieg.

Skull base lesion treatment can be facilitated by an image guidance system that allows surgeons to confirm the anatomic location of the tumor before operating. This "stealth" image guidance system uses magnetic resonance imaging or computed tomography scans taken presurgically to produce a 3-dimensional model of the skull. Surgeons use the 3-dimensional image as a navigational map during tumor resection. Thus, a safer and more complete excision of the tumor can be achieved, possibly offering the patient a better long-term prognosis.

When the risks of aggressive microsurgery are deemed too great, the Hospital has one of the country's most comprehensive radiosurgical programs. These procedures have been "very effective and safe for treatment of many types of skull base tumors that cannot be resected without irreversible damage," said Michael Sisti, MD.

Radiosurgery options available to patients include Gamma Knife; 3-dimensional intensity modulated radiation therapy, in which radiation is shaped to correspond precisely to the target site, using varying beam-intensity modulation technology; and linear accelerator-based radiosurgery, which utilizes a single, highly focused beam, applied in multiple passes.

"These techniques in combination are excellent adjuncts to the noninvasive management of skull base tumors," Dr. Sisti said. "We can recommend a treatment course more evenhandedly than might be the case in institutions where only one technology is available."

The complexity of the skull base region once rendered many tumors inoperable. However, because of advances in microsurgery and radiological imaging, many more tumors are treatable than in the past. At the same time, improvements in surgical technique and adoption of radiosurgical modalities have dramatically reduced complication rates. Despite the progress, skull base surgery remains complicated and risky for many patients. Thus, the skill and experience of the treating clinician is an important factor to consider. According to Steven Isaacson, MD, NewYork-Presbyterian Hospital provides an "unprecedented level of service" to patients and referring physicians. "We have neurosurgeons, radiation oncologists, clinical neuropsychologists, diagnostic neuroradiologists, and others, all of whom enjoy a healthy clinical relationship. We believe this translates into better outcomes for our patients."

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NEWYORK–PRESBYTERIAN
Neuroscience

New Technologies for Evaluating Tumor Response

NewYork-Presbyterian Hospital investigators are moving forward with research that may help establish magnetic resonance spectroscopy as an imaging modality complementary to magnetic resonance imaging, for evaluating cerebral tumor response to therapy.

"Potentially, the efficacy of different types of therapy could be evaluated based on metabolite changes seen with magnetic resonance spectroscopy," said Casilda Balmaceda, MD. Magnetic resonance spectroscopy has also been proven successful at consistently identifying metabolic changes in cerebral tumors, according to Pina Sanelli, MD.

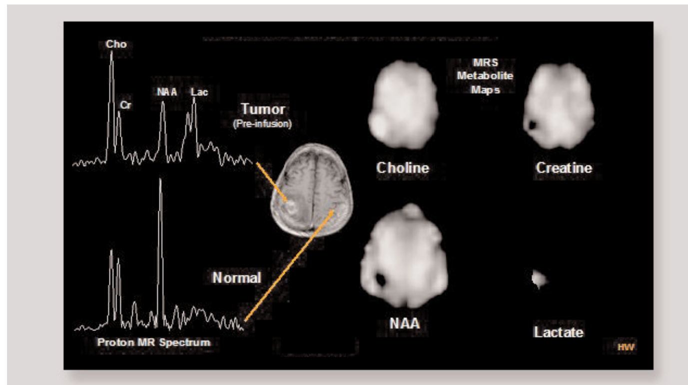
Metabolites commonly observed in magnetic resonance spectroscopy include choline (Cho), the levels of which are increased in tumor regions. High levels of choline indicate high levels of cell membrane production or breakdown in the region of interest. Other common metabolites observed in magnetic resonance spectroscopy are creatine (Cr), lactate (Lac) and N-acetyl-aspartate (NAA), the latter of which is thought to exist only in neurons and is decreased in regions of viable tumor. Lactate may also be increased in tumor as a result of increased anaerobic glycolysis, a preferred metabolic pathway for glucose in tumor tissue.

"Magnetic resonance spectroscopy will provide information on the heterogeneity patterns of these metabolic levels in tumors," Dr. Sanelli said. "The spectral pattern may also give useful information in estimating tumor regression or progression, by following changes in the metabolic peaks over the time course of the treatment."

Currently, magnetic resonance imaging with contrast material is the gold standard for assessing treatment efficacy in central nervous system cancers. However, it may underestimate the true extent of a tumor; in some studies, abnormal magnetic resonance spectroscopy findings have been detected outside of contrast-enhanced tumor boundaries delineated by standard imaging. In addition, magnetic resonance imaging is relatively insensitive in distinguishing recurrent tumor from normal postoperative changes (ie, edema or radiation-induced necrosis). Thus, NewYork-Presbyterian Hospital researchers believe magnetic resonance spectroscopy may enhance the clinical decision-making ability of physicians.

> *"In the past, the focus has been on what's going on in the tumor, not in the area where the tumor has been removed."*
>
> *—Susan Pannullo, MD*

Direct Infusion Brain Tumor Chemotherapy



Magnetic resonance spectroscopy has been proven successful at consistently identifying metabolic changes in cerebral tumors. Further, the efficacy of different types of therapy could potentially be evaluated based on metabolite changes seen with magnetic resonance spectroscopy.

"By evaluating metabolite levels and anatomical structure, it can provide information on whether or not a tumor is actively metabolizing," said Dr. Balmaceda.

Magnetic resonance spectroscopy can predict tumor change—prior to change evident on magnetic resonance imaging—in glioma patients treated with chemotherapy. They also found that an increase in a specific metabolic ratio seen on magnetic resonance spectroscopy, was a significant predictor of poor outcome.

Dr. Balmaceda helped plan a clinical trial that will be the first to use magnetic resonance spectroscopy to evaluate response to Gliadel wafer implantation, in malignant glioma patients. Magnetic resonance spectroscopy will be used as a primary indicator of therapeutic response to Gliadel in patients with newly diagnosed high-grade malignant glioma. Patients will be evaluated with magnetic resonance imaging and magnetic resonance spectroscopy at 21 days and 12 weeks after Gliadel insertion, with follow-up continuing until disease progression or death.

"In the past, the focus has been on what's going on in the tumor, not in the area where the tumor has been removed," said Susan Pannullo, MD. "We want to figure out what's going on in the area around where the tumor was taken out, and see what we can do to prevent it from coming back."

Clinical studies suggest that Gliadel may improve survival in some early-stage glioma patients. Now, the results of magnetic resonance spectroscopy studies may help determine specifically which patients may benefit from this particular therapy.

This is not the first time NewYork-Presbyterian Hospital investigators have evaluated magnetic resonance spectroscopy for central nervous system tumor progression and response to therapy. One recent study included malignant glioma patients receiving temozolomide chemotherapy. Investigators, including Dr. Balmaceda, Dr. Pannullo, and Dr. De La Paz, found that magnetic resonance spectroscopy may be complementary to magnetic resonance imaging; for example, in one patient, magnetic resonance imaging remained stable over time, while magnetic resonance spectroscopy revealed improvement in regions of interest. Now, Robert De La Paz, MD, in collaboration with neurosurgeon Jeffrey Bruce, MD, plans to use magnetic resonance spectroscopy to evaluate infusion of topotecan chemotherapy directly to the brain tumor.

"The rationale is that we can deliver a higher dose of chemotherapy to the tumor, while limiting its effect on the normal brain," Dr. De La Paz said.

Investigators are also looking at longer-term response to therapy in brain tumors, using magnetic resonance spectroscopy. In one recent group of patients, increased lactate was thought to be an early predictor of tumor recurrence or treatment failure.

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Gamma Knife

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areas of the brain can be treated in which surgery would be ineffective. Many conditions that were once considered inoperable can now be treated without an incision and with little or no pain. Indications include primary brain tumors, such as glioblastomas, benign brain tumors, such as meningiomas, and tumors involving other areas of the central nervous system, such as acoustic neuromas. The modality is particularly useful for patients with tumors that are not amenable to open surgery, patients for whom surgery is contraindicated because they have comorbid conditions or are taking specific medications, and those who simply are unwilling to undergo an open procedure. "It is an excellent treatment modality for brain metastases, allowing cancer patients to move on quickly to treatment of their systemic disease," said Susan Pannullo, MD. Arteriovenous malformations (AVMs) and trigeminal neuralgia can also be treated successfully in selected patients. The uses of the Gamma Knife are expanding further. Gamma Knife surgery is being investigated by NewYork-Presbyterian Hospital researchers as an alternative to conventional epilepsy surgery. In addition, the modality may one day prove useful to treat obsessive compulsive disorder, chronic pain syndromes, obesity, and other disorders.

At the initial consult, the radiation oncologist and/or neurosurgeon determines whether Gamma Knife treatment is appropriate for the patient. A registered nurse reviews the procedure with the patient and provides a tour of the unit. The patient also meets the Gamma Knife staff and is given the opportunity to ask questions before the actual treatment date.

Patients undergoing treatment are first fitted with a stereotactic head frame, which allows precise localization of the tumor or other target. Then, imaging is performed to determine the size and position of the abnormality. With this data, the multidisciplinary team plans the treatment, including the target area and the radiation dosage to be administered.

The patient's head, still secured in the stereotactic head frame, is positioned in a collimator helmet, which directs radiation to predetermined points in the brain. The patient is then slid into a large, shielded sphere containing the source of radiation. A series of short

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> *"Our commitment is to provide all the possibilities of modern medicine to help our patients. Through close, personal attention to individual patient needs, we have created an environment dedicated to providing complete supportive care and promoting optimum healing."*
>
> *— Michael Sisti, MD*

Gamma Knife

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exposures (approximately 10 minutes each) are applied with little or no discomfort to the patient, who can typically go home the same day.

Gamma Knife surgery is not appropriate for every neurosurgery patient and every indication. Thus NewYork-Presbyterian Hospital has adopted a multidisciplinary, multimodality approach to patient care. “Whereas most hospitals have either Gamma Knife or linear accelerator radiosurgery, we have both options,” said Michael Sisti, MD.

The Gamma Knife technology can provide outstanding results in a wide variety of indications. However, the technology is “the means and not the end” of efforts taken to improve patients’ lives, according to Dr. Sisti.

"We remain dedicated to the belief that the quality of the physician-patient relationship defines the excellence of care we wish to practice," he said. "Our commitment is to provide all the possibilities of modern medicine to help our patients. Through close, personal attention to individual patient needs, we have created an environment dedicated to providing complete supportive care and promoting optimum healing."

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