The Emerging Field of Neurosurgical Oncology: Novel Techniques to Optimize Outcomes and Minimize Mishaps

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Neurosurgical oncology is one of the most exciting areas of neurosurgery.[7,11,14] It deals with an interesting range of pathologies—*Figure 8.1* presents the breakdown of tumor types in 5230 brain tumor procedures performed by the senior author (PB) from 1987 to 2007. This paper will discuss three aspects of neurosurgical oncology—its justification as a subspecialty; the way in which new clinical technologies are creating increasingly safe manipulations to remove brain tumors; and the continuing importance of scientific discovery in this field. It will primarily discuss gliomas, because meningiomas are the topic for another paper in this volume. This subspecialty beautifully illustrates the themes of this meeting—transcendental leadership in clinical care, research, and education. In our reference list, we will primarily cite references from our own group and collaborators because of space restrictions; there are many hundreds of investigators working in these areas whose papers would have to be included to be a comprehensive account.

We begin with an illustrative case, that of a 21-year-old woman from a European country who came to see the first author with intractable seizures and a left medial frontal mass in the leg area of the cerebral cortex (see *Fig. 8.2*). She had tried multiple medications to control her seizures and found them less and less useful. Her social and academic lives were being destroyed by these seizures, occurring many times a day, and involving the right arm and leg and speech. The challenge, of course, was how to identify and remove this lesion without leaving her with leg weakness.

We approached this tumor with intraoperative magnetic resonance imaging (MRI) scanning with the General Electric (GE) Signa system, at the Brigham and Women's Hospital (BWH). We have used this system for more than 1000 tumor craniotomies and it is a very accurate device to identify and resect intracranial masses (it is further discussed later in this paper). Placing her in a prone position, we were able to dissect along the falx, identify the tumor, resect it, and verify that it was completely removed (*Fig. 8.3*). She awoke without deficit, left the hospital in 3 days, returned to her home country in 10 days, and has been seizure-free since her return.

This kind of result is now possible in neurosurgical oncology as we become increasingly able to use imaging and monitoring techniques for brain tumors of the cerebral cortex. It represents the most recent development in this important field.

NEUROSURGICAL ONCOLOGY AS A SPECIALTY

The history of neurosurgery and its leadership since the 1930s has been the gradual development of subspecialty areas, which have allowed committed practitioners to move their specialty forward in an important way; examples are pediatric neurosurgery, functional and stereotactic neurosurgery, cerebrovascular neurosurgery, and spine neurosurgery. Subspecialization allows not only more expert clinical care but also advances relevant research.

Neurosurgical oncology is now well enough developed as a specialty to be recognized as a separate enterprise. Neurosurgical oncology is that specialty of neurosurgery that deals with the medical and surgical treatment of patients with tumors of the brain, cranium, spinal cord, spine, and peripheral nerves.[16] It is certified as a neurosurgical subspecialty by the Society of Neurological Surgeons, with particular requirements for training.

Harvey Cushing was the first true neurosurgical oncologist.[6,8,9] He is the embodiment of transcendent leadership in clinical, scientific, and mentoring roles. His clinical contributions include an emphasis on outcome improvement, safe surgery, electrocautery, closure of the galea, and other technical improvements.[19,20] In neurosurgical neuroscience, he did pioneering work in glioma and meningioma biology. In addition, in training, he created a cadre of trainees who went on to form the new field of neurosurgery and, particularly, further developed brain tumor surgery.[8] In all of these areas, he transcended what had been previously accomplished.

Regarding the management of brain tumors, he wrote: "There is no therapeutic problem in medicine the successful approach to which requires an apprenticeship in so many fields. . . A primary training in surgery is desirable. . . . The specialized technique necessary for the safe and delicate

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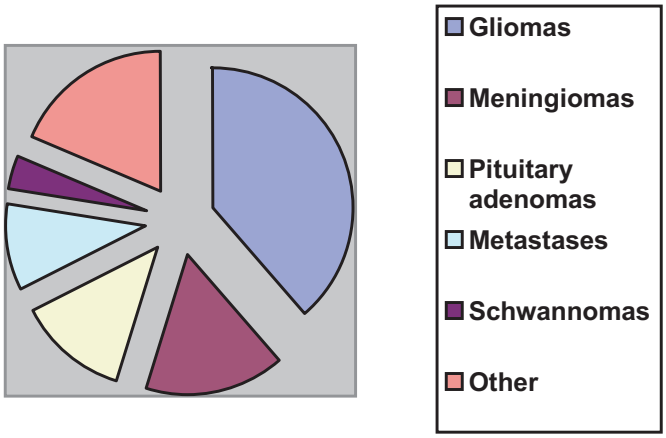

FIGURE 8.1. Types of brain tumor in a surgical series of 5000 cases (PB).

handling of the central nervous tissues. . . more than an amateur's knowledge of neurology. . . And a thorough familiarity with the gross and microscopical pathology of the lesions".[20]

Neurosurgeons have had a particularly important role in neurosurgical oncology. The Joint Section on Tumors of the American Association of Neurological Surgeons celebrated its 20th anniversary in 2005. Among its chairs have been Mark Rosenblum, Dennis Bullard, Peter Black, William Chandler, Mark Bernstein, James Rutka, Joseph Piepmeier, Raymond Sawaya, and Ronald Warnick. These are all distinguished leaders in neurosurgery, generally, as well as in tumor treatment. The *Journal of Neuro-Oncology* was founded by neurosurgeons to provide a forum for basic science papers on brain surgery at a time when many cancer journals were not interested in these. Neurosurgeons Michael Walker, Paul Kornblith, and Joseph Peipmeier have been editors of this important initiative. Recently, as neuro-oncology has become its own specialty of oncology, neurosurgeons have played a major role nationally and internationally; among others, Mitch Berger and Ab Guha in the Society for Neuro-Oncology in the United States; Ed Laws in the American College of Surgeons; David Thomas, Manfred Westphal and Jorg Tonn in the European Association of Neurooncology; Kintomo Takakura and many others in Japanese neurosurgery; and Andrew Kaye in Australia. These dedicated neurosurgeons and colleagues too numerous to mention have become spokespersons for neurosurgical oncology in the wider community.

NEUROSURGICAL ONCOLOGY AT THE BWH

Neurosurgical oncology as a subspecialty has an especially strong tradition at BWH. Harvey Cushing, surgeon-in-chief from 1913 to 1933, founded the enterprise at BWH and created the model of attacking tumors on two fronts, the surgical and the biological.

There have been other important events in neurosurgical oncology at BWH.

1. First linear accelerator (LINAC) radiosurgery in North America with Ken Winston, Bill Saunders, and Wendell Lutz in 1986.
2. First stereotactic radiotherapy with Jay Loeffler and Peter Black in 1991.
3. Pioneering imaging work of the surgical planning laboratory in navigation under Ron Kikinis, now continuing with Alexandra Golby.
4. World's first intraoperative MRI. The first craniotomy for brain tumor was performed by Peter Black in 1995 and since then there have been more than 1000 procedures carried out in it by the tumor surgeons at the BWH.[12,13]
5. World's first focused ultrasound procedure for brain tumor performed through an intact cranium in 2006—Ferenc Jolesz and Peter Black.

Our group operative experience has been very extensive, with more than 300 craniotomies for tumors per year and a database detailing more than 7000 patients with brain tumor craniotomy.

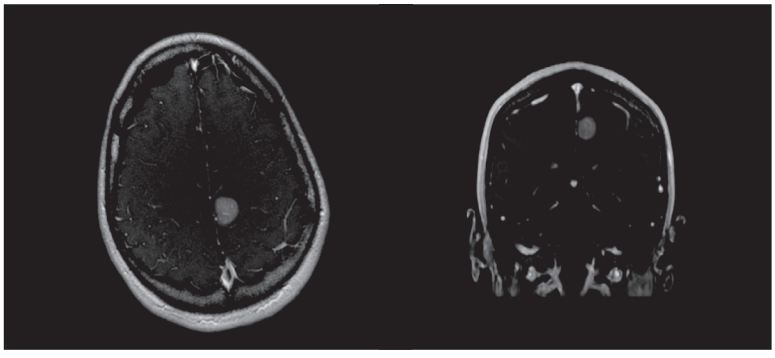

FIGURE 8.2. Preoperative transaxial and coronal gadolinium-enhanced MRI scan of a patient with a gangliocytoma of the postcentral gyrus.

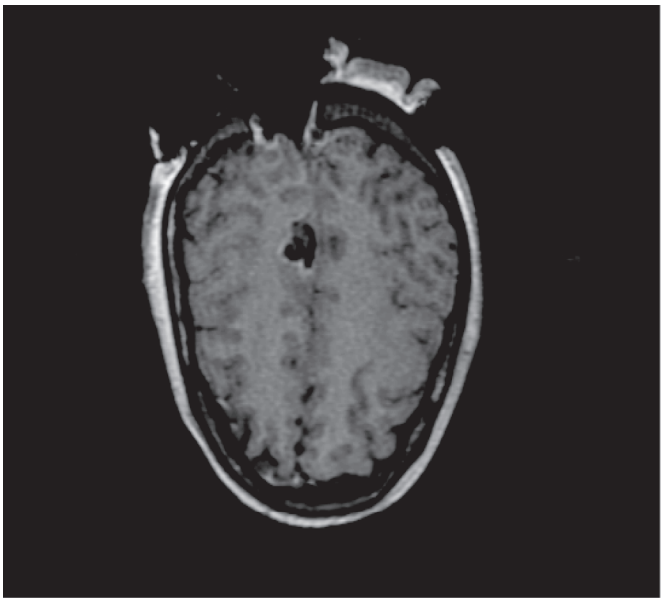

FIGURE 8.3. Intraoperative images taken in the GE scanner during and immediately after (the patient has been placed in a prone position).

NOVEL TECHNIQUES TO OPTIMIZE OUTCOMES AND MINIMIZE MISHAPS

Neurosurgical oncology as a field has steadily improved patient care through the development of a number of important techniques. These include microneurosurgery, with cranial base surgery, transsphenoidal surgery, pineal region, foramen magnum, and ventricular tumor surgery all being part of microneurosurgery; radiosurgery; and endoscopy. These technical developments have markedly improved our ability to take care of patients with brain tumors during the past generation. Because they are now part of routine care, we will not discuss them further here. We also will focus on glioma surgery and science rather than craniopharyngiomas, schwannomas, pituitary tumors, or pediatric tumors, all of which are important.[10]

In the past 10 years, there have been five further initiatives that are extremely important in this field. These initiatives essentially open the cerebral cortex as a safe area for brain tumor surgery:

1. New imaging techniques for preoperative brain mapping.
2. Intravenous sedation anesthesia.
3. Minimally invasive image-guided surgery, including intraoperative imaging.
4. Improved molecular understandings of brain tumors.
5. New therapeutic concepts and delivery routes.

NEW IMAGING TECHNIQUES AND PREOPERATIVE BRAIN MAPPING

Our group, along with several authors at other sites, demonstrated that cortical mapping can be a major technique to allow safe and complete resection of a tumor even from eloquent brain.[5] Our service has performed mapping on more than 1000 cases. Recently, this approach has been combined with brain imaging.

Brain imaging has made enormous strides in the last decade. Particularly important for surgical planning are segmentation, functional MRI (fMRI), and diffusion tensor imaging (DTI).[17,25,26,31] Using segmentation, it has been possible to develop paradigms that allow accurate modeling of a tumor mathematically.[17,26]

fMRI assesses the change in blood flow in the cortex that accompanies a particular activity, such as arm or hand movement or speech.[15,57] It requires sophisticated paradigms for both the testing and analysis of data and is largely a statistical enterprise. fMRI is noninvasive, does not require exposure to ionizing radiation, and can be readily repeated to follow clinical changes.

The ability to create fMRI paradigms that accurately allow assessment of movement, speech, memory, and vision is a difficult task requiring a dedicated group of imagers, engineers, and cognitive neuroscientists. The Golby laboratory (www.Golbylab.bwh) at BWH is such a group. Despite the usefulness of fMRI for creating preoperative maps of patient's individual functional brain anatomy, fine-grained comparisons to the gold standard of electrocorticography are few, particularly for language mapping. There are multiple factors contributing to the difficulty of making preoperative fMRI a reliable and useful method for defining eloquent cortex. If fMRI is to become a tool with sufficient sensitivity to predict clinical outcomes, it must provide information that is at least as spatially precise as the electrical cortical stimulation (ECS) standard. The Golby group brings together researchers from various fields to develop reproducible behavioral paradigms, high-resolution techniques for presurgical fMRI acquisition and analysis, and to accurately coregister data sets from fMRI and ECS to intraoperative anatomic MRI scans[15,57] (*Fig. 8.4*). They are particularly interested in motor, visual, speech and memory functions. Integrating such information into intraoperative neuronavigation, including intraoperative MRI scanning, allows the quantitative comparison of fMRI to ECS as well as providing information to the surgeon in the operating room.

Understanding white matter tracts using DTI provides critical information in surgical brain mapping. Diffusion of water is limited by the presence of myelin and axonal membranes, therefore, directionality of white matter tracts can be inferred from studies of water diffusion patterns. For this, magnetic field gradients are applied in multiple directions and

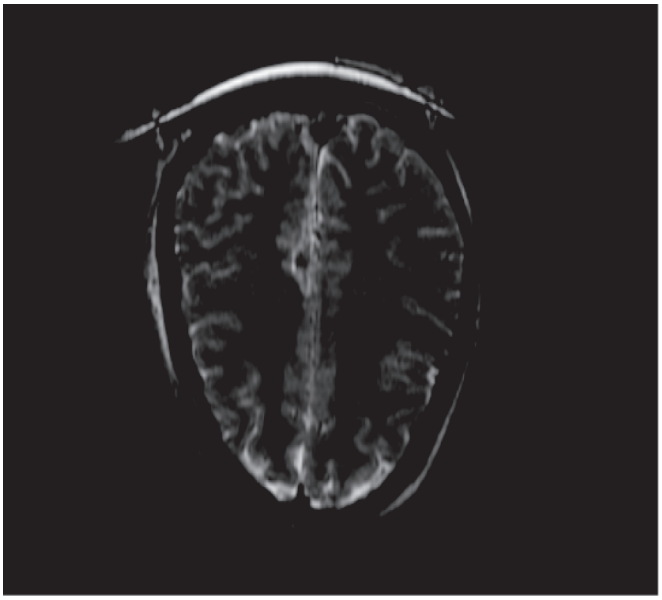

FIGURE 8.4. fMRI for speech function in a patient with a left frontal and insular low-grade glioma. R, right; L, left; A, anterior; S,; P, posterior.

a mathematically modeled matrix (diffusion tensor) determines the direction of greatest diffusion. The results are analyzed and used to create a principal eigenvector map, which parallels the local fiber direction. This map is visualized as a vector field and can be superimposed onto a structural image, such as a high-resolution weighted MRI scanning. The corticospinal and corticobulbar tracts (motor), arcuate fasciculus (language), and optic radiations (visual) can be modeled by DTI (*Figs. 8.5* and *8.6*).

One potential added use of DTI in neurosurgery is to distinguish between infiltration and edema in the peritumoral region. Two quantities derived from the tensor, the fractional anisotropy (FA) and the mean diffusivity (MD), have been measured in this region. FA quantifies the anisotropy of water diffusion. The FA indirectly measures tissue organization (high FA corresponds to fibrous tissue with one orientation, and low FA is caused either by tissue disorganization, such as in infiltration, by crossing fibers, or by high water content). MD quantifies the total amount of diffusion, which is mainly determined by the water content. MD is approximately constant in white and gray matter but increases with edema. A drop in FA relative to normal tissue can be caused by infiltration of tumor or by increased water content, hence, the relationship between FA and MD in the peritumoral region is of interest. Further investigation along these lines will likely lead to improved understanding of the relationship between brain tumors and adjacent white matter.

This laboratory has also strategies to calculate laterality indices from fMRI scan activations, particularly those related to memory encoding and language tasks. This group has developed novel analytic approaches to determining the relative asymmetry of activation using statistically weighted voxel distributions.

Information from fMRI, DTI, and other mapping modalities (such as magnetoencephalography) may be combined and coregistered into multimodal data sets, which can provide a more complete understanding of the functional anatomy than any one technique alone. In addition, together with engineering colleagues, this group is working on measuring and modeling brain shift and incorporating these deformations into the model as surgery progresses.

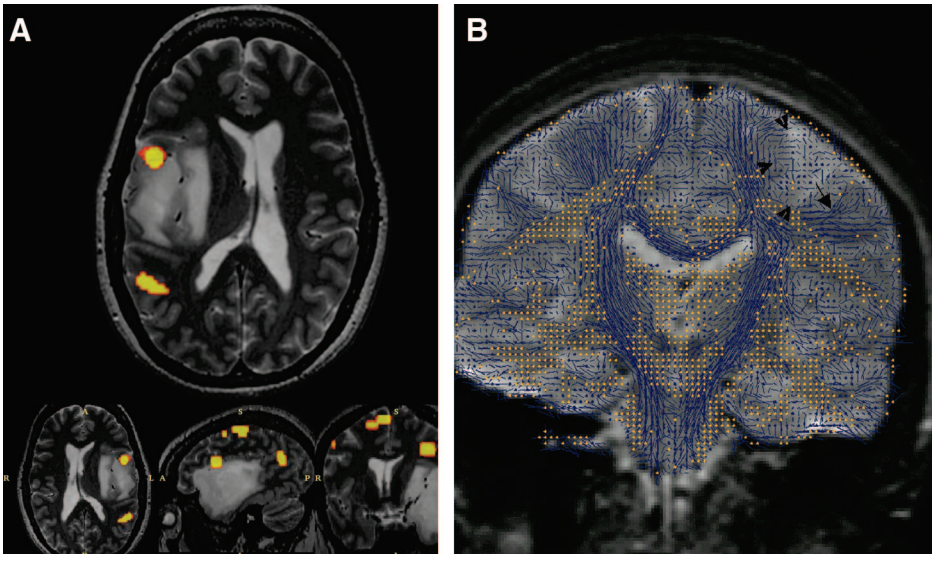

FIGURE 8.5. DTI combined with fMRI and segmentation to show the tumor (*green*), motor cortex (*yellow*), and the corticospinal tract displayed by DTI (courtesy Golby lab).

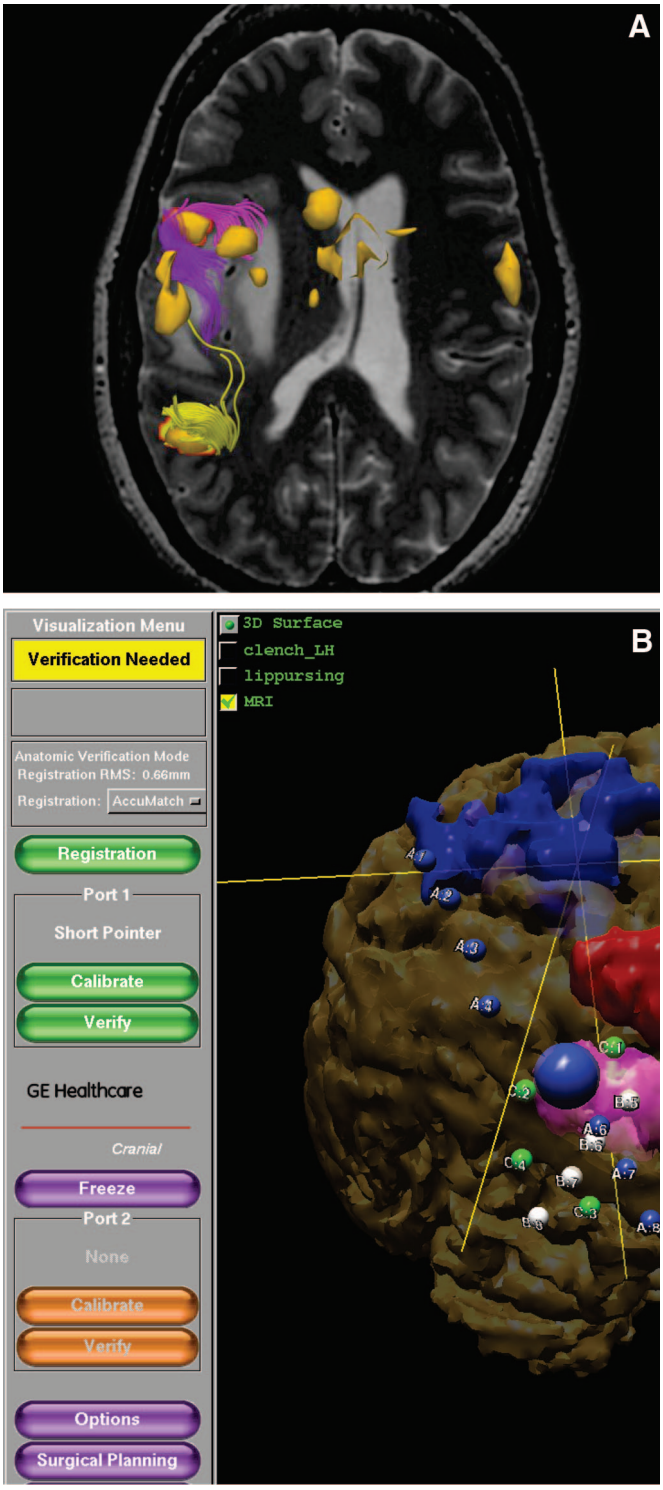

FIGURE 8.6. Intraoperative use at BWH of fMRI and ECS brain mapping for localization of eloquent cortex. *A*, intraoperative imaging demonstrates co-registration of preoperative fMRI motor mapping data (*red*) with updated MRI scan of brain and probe position. *B*, intraoperative photograph showing ECS mapping with markers indicating areas that have been tested.

INTRAVENOUS SEDATION ANESTHESIA

Danks et al.[21] reported a retrospective review of 157 consecutive adult patients who underwent craniotomy under local anesthesia by one surgeon (PMB) at BWH. All patients had tumors in close proximity to eloquent cortex (speech, motor, primary sensory, or visual cortex). In most cases, the lesion was considered inoperable by the referring surgeon. All resection was verified by postoperative imaging approximately 1 month after surgery, and all cases were reviewed by an independent neurosurgeon.[7]

Of patients, 80% had major resection despite the close relationship of tumor to eloquent cortex. Radiological gross total resection was achieved in 57% of patients and greater than 80% resection was achieved in 23% of patients. In 13% of patients, resection could be performed but less than 80% of tumor was removed because of danger of neurological deficit. In 7% of patients, only a biopsy could be performed because of infiltration in eloquent cortex that could only be assessed at surgery.

In 76 patients with preoperative neurological deficits, there was complete resolution of these deficits in 33% patients, improvement in 32% patients, no change in 28% patients, and long-term worsening in 8% patients. Among 81 patients with no preoperative neurological deficit, 1 patient suffered a major permanent neurological deficit, and 2 patients developed minor deficits. There was a transient postoperative deficit in one-third of cases, but this had resolved at 1 month in all but three patients. Statistically, therefore, it seemed to be better to take this kind of tumor out of a patient before they have a deficit.

Patient satisfaction with the procedure was good.[22] Only one case needed to be converted to general anesthesia. Operating time and hospital stay were lower than the mean for brain tumor craniotomy at this hospital.

These data and work from other groups suggest that surgery under intravenous sedation anesthesia provides a safety margin that is very important in carrying out successful tumor resection. Despite the advances in non-invasive imaging described above, intraoperative testing provides the most reliable and validated assessment of functional cortex.[42] Nevertheless, non-invasive functional imaging may be very useful in optimizing the deployment of intraoperative testing, or in patients who may not tolerate awake surgery.

NAVIGATION IN THE TRADITIONAL OPERATING ROOM

In 1989, we demonstrated that a simple CRW frame could be used as a navigation system for tumor craniotomy as well as for biopsy and lesion making in the brain, avoiding systems of frame-based maneuvering that are more expensive.[44] Since then, there has been an extensive development of navigation systems that are frameless and accurate. Their

development is one of the remarkable applications of computer systems to brain surgery.[26]

There are many systems available in the traditional operating room, each with particular advantages.[2] They all have common features:

1. Preoperative acquisition of MRI or computed tomographic scans by specific protocols.
2. Reconstruction capacities with differing sophistication of segmentation of tumor.
3. A registration system that includes scalp fiducials or surface-to-surface registration.
4. A navigation system that links the computer with the actual image. We have used the Instatrak system from GE, which uses an electromagnetic system rather than a visual system. This type of system does not require line-of-sight, thus, allowing the surgeon to avoid blockage of navigation by physical obstruction caused by the position of the patient, the surgeon, the microscope, or instruments.

Navigation in the operating room has made a difference for metastatic tumors, convexity meningiomas, and glioblastomas. For metastatic lesions, for example, Tan and Black[55] demonstrated that image-guided surgery allowed resection of a metastasis in an eloquent area with resolution of preoperative deficit in 75% of patients. Navigation allows accurate localization of a mass if there has not been brain shift when the time comes to localize it. This means that tumors that once required large craniotomy flaps can now be resected with small linear incisions. If the mass is of different texture or consistency from the brain, a navigation system is all that is needed to localize it. The surgeon can then remove it using tactile and visual cues to distinguish it from brain.

INTRAOPERATIVE IMAGING

For a number of reasons, it became clear in the late twentieth century that intraoperative imaging would add significant value to brain tumor procedures.[2] These reasons include:

1. *Brain shift:* brain parenchyma, cerebrospinal fluid and blood vessels shift during neurosurgical procedures, rendering preoperative MRI scans unreliable.[47]
2. *More accurate navigation including brain biopsy:* with intraoperative imaging, brain biopsies, regardless of the location of lesion, can be performed safely and with high accuracy. The advancement of the biopsy needle within the substance of the brain can be followed by the neurosurgeon in nearly real time.[46]
3. *Monitoring of intraoperative brain changes:* MRI scanning systems enable the neurosurgeon to visualize and correct intraoperative changes. Progression of surgery can be followed and the global status of the brain can be checked in case of an intraoperative complication, such as intracerebral hemorrhage, diffuse cerebral edema, or hydrocephalus.
4. *More complete resection:* there are numerous recent studies demonstrating improved surgical outcome with intraoperative imaging. Low-grade gliomas and complex pituitary adenomas are examples of such tumors.

The system we use for intraoperative imaging is the GE Signa System, an open MRI scan design allowing navigation in real time within the magnet.[2,12,13,39,41,45,48] The patient is managed in precisely the same way as in a traditional operating room; all instruments and anesthesia equipment are nonferromagnetic. The result is that the surgeon has MRI scan vision with the capacity to immediately confirm surgical effect. The device is housed within a magnetically shielded surgical suite with MRI-compatible neurosurgical instruments and equipment for monitoring. An MRI-compatible microscope can be positioned between the magnets and over the shoulder of the surgeon.

Confirmation of the extent of resection, accommodation to intraoperative changes, and monitoring of potential intraoperative complications are routine with craniotomies performed in this device. A light emitting diode-based navigational system is an integrated component of the MRI unit and provides tracking capabilities within the three-dimensional space at the center of the magnet. A craniotomy is performed in a standard fashion; operating within the magnet does not limit the surgeon's ability to perform the procedure. The size of the bone flap and dural opening can be decreased with an assurance that adequate exposure will be achieved. Accuracy in the localization, targeting, and guidance of the resection is maintained as these anatomic changes occur by constantly updating images and correlating this with the surgical field of view. This system acts as a stereotactic frame that allows real-time monitoring of probe placement and a novel way of evaluating surgical resection.

This same navigation feature makes it especially valuable when performing brain biopsies. The biopsy probe can be followed as the lesion is entered, and the surgeon can be certain that he or she is in pathological tissue by imaging and that there is no postoperative bleeding or major injury to brain after the biopsy probe has been removed. We have performed more than 200 biopsies with safe and accurate results; the details for a smaller initial group have been published.[46]

Our group has performed more than 1000 craniotomies in the GE intraoperative scanner.[2,11,13,40,41,43,46,49] Pathological diagnoses have included glioblastomas, anaplastic gliomas, low-grade gliomas, astrocytomas, oligodendrogliomas, gangliogliomas, pineoblastoma, meningiomas, and metastatic lesions.[51] Patients whose tumors are particularly appropriate for resection in the intraoperative MRI scanning include:

1. Patients with primary gliomas in or adjacent to sensitive cortical areas, such as the sensory or motor strip, where knowledge of the tumor extent and location is critical. This is particularly important for low-grade gliomas whose margins may not be adequately visualized in any other way. We have shown a diminished mortality in patients with low-grade gliomas whose tumors could be resected "completely" with this technique, and an improvement in survival with use of intraoperative MRI scanning compared with other modalities.[18]
2. Patients with deep lesions difficult to biopsy in the white matter or brainstem in whom the trajectory of the approach must be optimized and confirmation of target entry is critical.
3. Patients with small intraparenchymal lesions that might be difficult to accurately locate with other systems.
4. Patients with recurrent gliomas that blend with surrounding tissue.
5. Patients with cranial base and pituitary tumors, especially if they are recurrent.

The clearest indication of the importance of intraoperative MRI scanning is its rapid adoption by leading neurosurgical centers internationally. There are now more than 60 intraoperative MRI scanning systems being used around the world. The Siemens Magnetom System moves the patient into and out of the MRI scanner on a rotating bed. Steinmeier et al.[52] have used this with both a 0.2-T scanner and a 1.5-T MRI scanner. The Hitachi and Philips systems are examples of this concept as well. A second type of system brings the scanner to the patient. The best example of this is IMRIS, in which the 1.5-T intraoperative MRI scanner is brought from a shielded cage into the region of the patient to obtain high-quality images and verify removal of tissue.[53] This is presently in use at the Children's Hospital Boston and has been a major help in assuring that surgery has accomplished what one expected of it. One advantage of this system is that the room can be used for traditional surgery when it is not being used for intraoperative imaging. A variant of this concept is the Odin PoleStar System, which acts as a fluoroscope and gives a limited view of the brain. This has modest navigational capacities but can be used within the traditional operating room. This is a very low-field (0.12 T) magnet, but may be useful for some applications.[39]

These different systems are different solutions to the same problems—how can we know with certainty where a brain lesion is, how do we know we have removed it, and how can we monitor the response to the surgical intervention as it is taking place? These developments lead the way for innovative new approaches to treat brain tumors.

INTRAOPERATIVE IMAGING FOR LOW-GRADE GLIOMAS

An important example of the way in which intraoperative imaging can change the approach to a disease is in the management of low-grade gliomas. It seems increasingly clear that radiation will not increase survival with these lesions and, many years ago, we set the goal of using surgery as the major treatment.

Recently, we reviewed the results of this approach for 156 consecutive patients undergoing surgical resection of a unifocal, supratentorial low-grade glioma in the MRI operating suite at BWH. Estimates of disease-free and overall survival probabilities were calculated using Kaplan-Meier methodology. The association between extent of resection and these probabilities was measured using a Cox proportional hazards model.

The death rates observed in these data were compared with the expected number of deaths using age- and histological-specific survival rates obtained from the Surveillance, Epidemiology, and End Results Registry.

Patients who underwent subtotal resection were at 1.4 times the risk of recurrence and 4.9 times the risk of death relative to patients undergoing gross total resection. Overall, the 1-, 2-, and 5-year age- and histological-adjusted survival rates for patients undergoing surgical resection using intraoperative MRI scan guidance were 1 year, 98.1%; 2 years, 96.4%; and 5 years, 82.4%.

These rates included patients who could not have complete resection. These were significantly better than those reported using national databases. From our experience, algorithms can be developed that describe surgical risk for resection of a low-grade glioma.[54]

Novel Ablative Technologies—Interstitial Laser Therapy

Following along the concept of minimal invasion, there are several technologies that are now being developed that may further change our capacity to deal with specific tumors. One of these is laser hypothermia, in which a Neodymium-Yag laser fiber is introduced to the center of a lesion. The changes that occur with heating can be followed, and the patient can have complete destruction of the lesion. To date, this has been performed for deep metastases, for gliomas, and for a hypothalamic glioma.[30]

Novel Ablative Technologies—Focused Ultrasound

A second future potential therapy is focused ultrasound. With the capacity to calculate differential absorption of energy through the cranium, it is possible to develop the technology of multiple-source high-energy ultrasound that can destroy a target non-invasively. This is still in the development phases, but may be an important addition as well.

IMPROVED MOLECULAR UNDERSTANDING OF BRAIN TUMORS

Neurosurgical oncologists are committed to pushing forward neurosurgical neuroscience in a variety of ways through basic, translational, and clinical research. We have written about meningioma science in another chapter, so we will focus here on gliomas.

To understand the treatment of gliomas, including glioblastoma, it is critical to understand their behavior. They have the ability to divide, to invade, to cause new blood vessel formation, and to cloak their activities immunologically. The ongoing development of glioma science can be seen as a continuum using previous findings to extend our knowledge. Thus, work performed many years ago on glioblastoma clonality is relevant to the present concept of precursor cells as being responsible for the development of glioblastoma.[24] Our laboratory (blacklab.bwh) has evaluated molecular attributes of tumors for many years. We showed long ago that the platelet-derived growth factor system was important in glioblastoma,[32,43] and that it seemed to create an autocrine mechanism, and that its receptors were activated in human tumors[27]; this only became relevant when Gleevec was created. Working with us and Charles Stiles of the Dana-Farber Cancer Institute, Turker Kilic was able to show that this selective inhibitor for platelet-derived growth factor and MYC had a significant effect on glioblastoma growth in vivo.[32]

Studies on angiogenesis become particularly important as we develop antiangiogenic agents; the concept of blocking blood vessel formation is an increasingly powerful one in brain tumor therapy .[33–35, 38]. Recently, with antiangiogenic agents reaching clinical trials, it is closing the chasm from bench to bedside. It may have important relevance to studies of the extracellular matrix as well.[3]

Molecular genetic techniques, such as differential display, microarray comparative genome hybridization analysis, and microarray ribonucleic acid studies, once considered important just as descriptors of the landscape for glioblastoma multiforme, are now used to make specific predictions regarding response to therapy.[32,37,40,56] Mark Johnson (johnsonlab.bwh) has a particular interest in this aspect of neurosurgical neuroscience. Telomerase, an enzyme important in regulating cell cycling, is potentially interesting for gliomas as we learn more about their division controls.[36]

NEW DELIVERY METHODS FOR ANTITUMOR AGENTS

The concept that therapies can be applied directly to the brain is a very important one in neuro-oncology. Traditionally, intravenous and intraarterial administrations have been considered the major techniques for delivery of chemotherapeutic agents. However, agents delivered in this way may have important systemic side effects and also require much greater concentrations of the therapeutic compound than might be needed with local application. This approach has been particularly pioneered by Henry Brem and the Hopkins group.

Application of therapeutic agents in local therapy—that is, therapy that works from the center of the tumor—is a particularly important alternative to systemic therapy for the neurosurgeon. Our laboratory has demonstrated the efficacy of a number of these techniques in animal models:

1. Slow-release microspheres embedded with chemotherapeutic agents. We have demonstrated that subcutaneous glioma tumor growth can be reduced by inhibitors of angiogenesis delivered locally using a controlled delivery system in the shape of microspheres composed of poly-l-glutamic acid.[50] For these studies, we used PF-4 as a protein that inhibits angiogenesis; poly-l-glutamic acid microspheres loaded with PF-4/CTF significantly inhibited intracranial human glioma growth. MRI scanning was used to monitor effects, including diminution of blood volume of tumor.
2. Intracerebral microinfusion. In another study, we compared the effects of endostatin delivered by daily systemic administration or local intracerebral microinfusion.[50] We used intracranial U87 human glioblastoma xenografts in nude mice. MRI scanning methods were used to assess treatment effects, and additional histopathological analysis of tumor volume, microvessel density, proliferation, and apoptosis rate were performed. Three weeks of local intracerebral microinfusion of endostatin (2 mg/kg/d) led to 74% ($P < 0.05$) reduction of tumor volumes with decreased microvessel densities (33.5%; $P < 0.005$) and a three-fold increased tumor cell apoptosis ($P < 0.002$). Our results indicate that the local intracerebral microinfusion of antiangiogenic compounds is an effective way to overcome the logistical problems of inhibiting glioma-induced angiogenesis.
3. Continuous release of endostatin from microencapsulated engineered cells for tumor therapy. These experiments again demonstrated the capacity of local therapies in the brain. Baby hamster kidney cells were stably transfected with a human endostatin expression vector and were encapsulated in alginate-poly-l-lysine microcapsules for long-term delivery of human endostatin.[28] The release of biologically active endostatin was confirmed using assays of bovine capillary endothelial proliferation and of tube formation. Human endostatin released from the microcapsules brought about a 67.2% inhibition of bovine capillary endothelial proliferation. A single

local injection of encapsulated endostatin-secreting cells in a nude mouse model resulted in a 72.3% reduction in subcutaneous tumor weight 21 days after treatment. This inhibition was achieved by only 150.8 ng/ml human endostatin secreted from 2×10^5 encapsulated cells.

4. Stem cells as a therapeutic delivery vehicle. Previous studies from our laboratory have demonstrated that when stem cells are injected into the brain around a tumor, human stem cells have the ability to track down human glioma cells, especially those that have migrated into the normal brain. Equipped with a "suicide gene", they can destroy their target once they track it down (*Fig. 22.7).*[1]

Other molecules can also be used in this stem cell model. During his research time in Boston, Lorenzo Bello, a neurosurgeon from Milan, identified a protein fragment called PEX that is naturally found in various tumors and is responsible for inhibiting tumor angiogenesis, tumor invasion, and tumor cell proliferation.[4] His studies clearly demonstrated that the administration of PEX resulted in a 99% inhibited of the growth of human malignant glioma cell lines grown in nude mice. Seung Ki-Kim, a neurosurgeon from Korea, evaluated the antitumor activity of PEX-producing human neural stem cells (NSCs) against malignant glioma. Histological analysis showed that PEX-transduced NCSs migrate to the tumor boundary and caused a 90% reduction of tumor volume.[29] Nils Ole Schmidt, a neurosurgeon from Germany, analyzed the in vitro and in vivo effects of angiogenic growth factors and protein extracts from surgical specimens of brain tumor patients on NSC migration. We demonstrated that vascular endothelial growth factor (VEGF) is able to induce a long-range attraction of transplanted human NSCs from distant sites in the adult brain. Our results indicate that tumor up-regulated VEGF and angiogenic-activated microvasculature are relevant guidance signals for NSC tropism toward brain tumors.

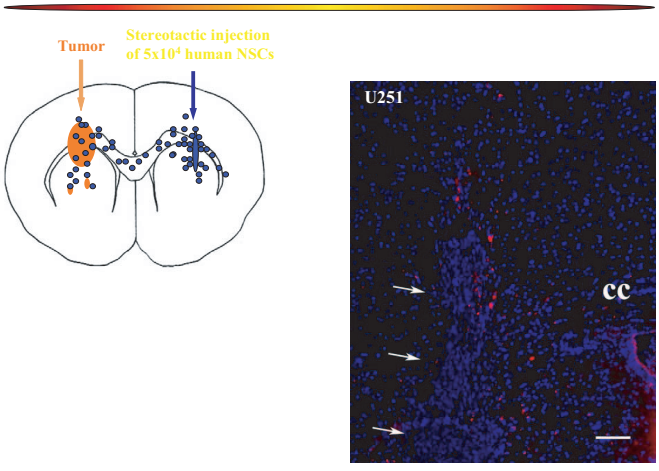

FIGURE 8.7. NSCs migrate through the brain to a VEGF target; cc, corpus callosum.

THE NEUROSURGEON AS LOCAL ONCOLOGIST

The concept of epicentric therapy is important because it places the neurosurgeon squarely at the center of future brain tumor chemotherapies and biological therapies.[23] The problem of getting therapeutic agents across the blood-brain barrier and of flooding the body with materials targeted at a small area of brain is a significant one. Epicentric therapy allows a focused and precise "minimally invasive" approach to the pharmacotherapy of brain tumors that may be as effective as the minimally invasive surgical techniques of our present era. It should be possible to use new cell cycle agents, anti-invasive agents, and gene therapies as local treatments. It seems particularly important that the glioma surgeon of tomorrow be interested not only in extirpation of a tumor but also in new delivery methods for destroying it with molecular biological techniques. In this way invasiveness and heterogeneity may be overcome "from the inside out," and the neurosurgical oncologist will be able to explore new frontiers of effective therapy. It is an example of the increasing need for neurosurgical oncologists to become molecular neurosurgeons as well as image-guided minimally invasive surgeons as they explore the next frontiers in this exciting field.

CONCLUSION

Neurosurgical oncology is an important, exciting, and mature field in neurosurgery. It has a tradition of complex technical achievement through microsurgery; to this has recently been added the ability to operate on the cerebral cortex safely through image-guided techniques and brain monitoring. The result is robust image-guided minimally invasive surgery that leads the neurosurgical field as well as other oncological specialties.

To this, we add the capacity to perform exciting and relevant research in basic, translational, and clinical fields. The output of the laboratories at the BWH during the past 10 years gives a small idea of the scope of the work—it includes papers on mechanism, on new therapies including local therapies, on a molecular analysis of the tumors, and preclinical studies. The science of neurosurgical oncology is as exciting and important as its surgical aspect. This is a technically challenging field with a major intellectual and scientific component.

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