Oncopolitics

Where Does the Neurosurgeon Fit in the Management of Brain Cancer?

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"Whenever a new scientific discovery is reported to the scientific world, they say 'It's probably not true.' Thereafter, when the truth of the scientific proposition has been demonstrated beyond question, they say 'Yes, it may be true, but it is not important.' Finally, when sufficient time has elapsed to fully evidence its importance, they say 'Yes, surely it is important, but it is no longer new.'"—Michel de Montaigne (1533–1592).

Increasingly, neurosurgeons have formed collaborative and collegial relationships with a wide variety of other surgical as well as nonsurgical specialists. Modern medical care often demands this, and most patients benefit greatly from this collaboration. Physicians, however, are frequently beset by difficulties in reacting to innovation in their field or to changes in medical or surgical paradigms. When skeptical behavior involving care of patients with tumors leads to obstruction of innovation, such behavior becomes part of a phenomenon we term "oncopolitics." Turf battles are natural parallels to oncopolitics. Oncopolitics frequently emerge when innovation threatens to change a manner of practice that is well established. Oncopolitics also rears up when innovation may lead to a significant economic impact either positively or negatively. Oncopolitics may threaten innovation when change comes too quickly or when there are sufficient long-term clinical outcome studies to justify its continued promulgation. Skepticism among surgeons is rampant and frequently appropriate. Surgical and medical histories are filled with theoretically effective therapies that are subsequently proven to have no merit. In this report, the authors describe six vignettes that illustrate the interaction of innovation and oncopolitics.

Innovation in Skull Base Tumor Management

Based on the pioneering work of Lars Leksell and his disciple, Georg Norén, the first patient with acoustic neuroma underwent stereotactic radiosurgery in 1969 using the first-generation Leksell gamma knife (Elekta Instruments, Inc., Atlanta, GA).[42] The impetus to develop such a technology, just as the benefits of the operating microscopes were first being applied, originated from the Swedish pioneer, Lars Leksell.[41] Leksell had been raised in an era of high morbidity for the management of cranial base tumors. Virtually all patients in the era of 1930 to 1965 had a facial palsy after conventional surgery for an acoustic neuroma. No patient had preservation of hearing. The gamma knife appeared to be a closed-cranium, bloodless way to inactivate, rather than remove, an acoustic neuroma. Georg Norén, under the watchful eye of Lars Leksell, was an early pioneer in the management of acoustic neuroma. Over the years, identification of the tumor became easier. Pneumoencephalographic outlining of the tumor borders was replaced by computed tomography and eventually by magnetic resonance imaging (MRI).

In the early 1980s, as we began our attempt to bring the first 201 Cobalt source gamma knife to North America, we immediately encountered much resistance from colleagues in other specialties.[47] One radiation oncologist wrote to the hospital CEO in 1983: "I don't know what the gamma knife is, but I am against it." The first patient treated with the gamma knife at the University of Pittsburgh on August 14, 1987 had an acoustic neuroma of moderate size. This patient did not want to have microsurgical removal of the tumor. At our center, Peter Jannetta and others had already pioneered microsurgical management of posterior fossa tumors, often with outstanding results.[34] Steadily improving results had also been reported by many other centers in North America, Asia, and Europe. The response to the potential use of gamma knife radiosurgery for acoustic neuroma was met with skepticism. Nevertheless, patients began to solicit advice about both microsurgical and radiosurgical options.

Microsurgically focused surgeons tended to tell their patients four things. First, the patient was told that it would not work. Second, they were told that even if it worked temporarily, eventually the tumor would recur and require surgical removal. Third, when surgical removal was attempted, the tumor

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would be scarred and adherent to the facial nerve leading to almost certain facial palsy. Fourth, even if any of these events did not materialize, the patient would eventually get some other cancer as a side effect despite the fact that this procedure delivered focused radiation in a single session. Oncopolitics was clearly in play. In the 1980s, there were very little long-term outcome data. Both our neuro-otologic and neurosurgical colleagues remained, with justification, wary. Our early reports, at the beginning of what turned out to be, in essence, a dose de-escalation strategy, revealed initial transient facial weakness rates of between 30 and 40%.[44,46] The doses selected were based on the 1969 to 1985 experience in Stockholm. In reality, those doses were too high and associated with unnecessary risks and no additional benefit. Marginal doses of 16 to 18 Gy were not necessary for long-term tumor growth control. By 1993, the dose was reduced to 12 to 13 Gy at the margin and successive studies continue to show excellent tumor control rates plus a continuing improvement in facial and hearing preservation. Despite new reports with current data, selected microsurgical colleagues continued to quote the early results of radiosurgery to patients, possibly to steer their decision in a microsurgical direction. As radiosurgical results continued to improve and follow-up continued to increase,[11,23,49,62] and as surgeons became familiar with the technique, such behavior tended to diminish.

In today's era, neurosurgeons are rarely the primary gatekeeper for patients with acoustic neuromas unless there is facial numbness from a large tumor astutely picked up by a neurologist who then refers the patient to a neurosurgeon. The majority of such patients are eventually referred to an otolaryngologist and some to a neuro-otologist. Usually, the initial examination is performed by such physicians, many of whom are trained to participate in the removal of cranial base tumors. Because their results with microsurgery continued to improve at the same time, various centers of excellence with high volumes of acoustic neuroma microsurgery were extremely dubious about the potential benefit of radiosurgery.

Similarly, patients with other types of cranial base tumors, including meningiomas of the petroclival region and the cavernous sinus region, pituitary tumors, schwannomas of the fifth or ninth and tenth cranial nerves, and even more aggressive neoplasms such as chordomas and chondrosarcomas became potential candidates for radiosurgery (*Table 5.1*).[10,17,39,55,56,68,76] Although most patients with pituitary tumors require and benefit from traditional transsphenoidal or endoscopic removal, many patients with incomplete removal or recurrent tumors, especially those laterally displaced in the cavernous sinus, are ideal cases for eventual management by radiosurgery. In the case of tumors in the cavernous sinus or clival region, significant morbidity often followed attempts at radical resection. In contrast, radiosurgery had excellent long-term tumor control rates with more than 96% of such patients having prevention of further growth at 10- and 15-year follow-up.[68] (*Fig. 5.1*)

TABLE 5.1. Indications treated with gamma knife radiosurgery at the University of Pittsburgh (1987–2007)

Brain Disorder	Number of Patients Treated
Vascular disorders	1303
Benign tumors	2753
Glial neoplasms	666
Metastatic tumor	2495
Functional targets	844
Miscellaneous tumors	318
Total	8379

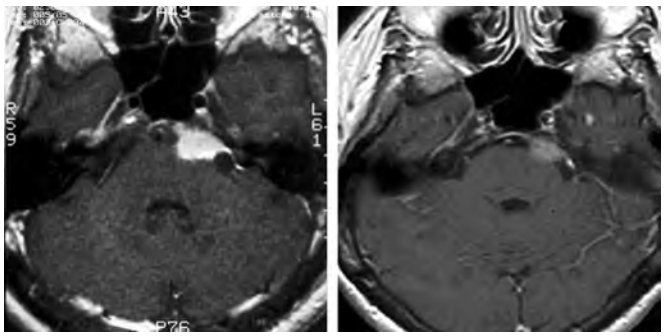

FIGURE 5.1. Preradiosurgical axial MRI scan of a petroclival meningioma (left) and 10-year follow-up MRI showing tumor volume regression (right). The patient had no cranial neuropathy.

During the late 1980s and early 1990s, advances in cranial base surgery became possible because of excellent surgical training, microsurgical skills, vascular reconstructive techniques, advances in neuroimaging, and improved postoperative critical care. These advances translated into better tumor removal and better outcomes. However, certain patients experienced new neurological deficits after surgery. In our experience, 60% of patients developed new neurological deficits after attempted microsurgical removal of cavernous sinus tumors despite remnants remaining afterward.[17] Some patients underwent even less beneficial "peek and shriek" surgical procedures.

We have continued to explore the benefit of radiosurgery in the management of a wide variety of cranial base tumors (*Table 5.2*). This includes experience in more than 1200 acoustic neuromas and 1000 meningiomas (*Table 5.3*). Experience expanded with other cranial base tumors, including pituitary tumors and other more aggressive tumors of the cranial base (*Table 5.4*). In some patients, radiosurgery represents an effective treatment for recurrent tumors, whereas in other cases, it was an effective primary strategy. The increasing availability of radiosurgical techniques greatly increased the number of tools accessible to the neurosurgical community and expanded treatment options for a wide variety of patients (*Tables 5.5 and 5.6*).

In addition to their primary role as the providers of fractionated radiation therapy, radiation oncologists are impor-

TABLE 5.2. Gamma knife radiosurgery for benign brain neoplasms at the University of Pittsburgh (1987–2007)

Brain Disorder	Indications	Number of Patients Treated
Benign tumors	Vestibular schwannoma	1262
	Meningioma	1149
	Pituitary adenoma	259
	Nonvestibular schwannoma	83
Total		2753

TABLE 5.3. Gamma knife radiosurgery for glial neoplasms at the University of Pittsburgh (1987–2007)

Indications	Number of Patients Treated
Astrocytoma	
Pilocytic	77
Fibrillary	40
Anaplastic	94
GBM	302
Other gliomas	
Astro-oligodendroglioma	9
Anaplastic astro-oligodendroglioma	31
GBM-oligo	7
Oligodendroglioma grade 2	11
Ependymoma	63
Medulloblastoma	21
Total	666

GBM, glioblastoma multiforme.

TABLE 5.5. Gamma knife radiosurgery for metastatic neoplasms at the University of Pittsburgh (1987–2007)

Primary Tumors	Number of Patients Treated
Breast	437
Sarcoma	16
Gastrointestinal	126
Kidney	199
Lung	1133
Melanoma	375
Nasopharynx	29
Thyroid	12
Others	104
Unknown primary	64
Total	2495

tant colleagues in the field of radiosurgery. Their field has changed dramatically with the development of image-guided radiation therapy (IGRT) using linear accelerators. To date, there have been no long-term outcome studies that compare fractionated radiation therapy techniques directly with radiosurgical outcomes, especially using the gamma knife. However, the data to date certainly provide no startling evidence of improvement in tumor control rates for tumors such as acoustic neuroma, in hearing or other cranial nerve preservation rates, or an increased safety profile.[2,8,9,13–15,21,24,33,35,37,52–54,60,63,64,71,74,77–81] Today, because of noninvasive fixation devices, single-treatment delivery of stereotactic radiation is no longer mandatory. The main advantage of stereotactic radiation is that it allows higher doses to be delivered to the tumor because of increased tolerance of the surrounding healthy tissues and surrounding tissues.

The advocacy of a particular technique is often related to the training bias of the individual surgeon, neuro-otologist, or radiation oncologist. Corporate relationships also may influence therapeutic choices. Radiosurgical procedures represent an enormous innovation that has been of benefit to a wide variety of patients who either had limited surgical options or the expectation of significant postoperative morbidity. As more specialists, including neurological surgeons, neuro-otologists, radiation oncologists, and medical physicists, have become familiar with radiosurgical options, the murmur of oncopolitics has diminished. This broader consensus has been engendered by hundreds of publications, presentations at national and international meetings, and long-term outcome data.

TABLE 5.4. Model showing effect of extent of surgery and radiation therapy on reducing the number of tumor cells in a glial neoplasm

No. of Cells Before Cytoreduction (30–60 g)	Extent of Tumor Resection	Log Reduction in Tumor Cells	Remaining Tumors Cells After Surgery	Log Kill by Radiation Therapy (55–60 Gy)	Remaining Cells After Radiation Therapy
$3–6 \times 10^{10}$	90%	1	$3–6 \times 10^{9}$	2	$3–6 \times 10^{7}$
$3–6 \times 10^{10}$	99%	2	$3–6 \times 10^{8}$	2	$3–6 \times 10^{6}$
$3–6 \times 10^{10}$	99.9%	3	$3–6 \times 10^{7}$	2	$3–6 \times 10^{5}$

Modified from concepts of Shapiro.[65]

TABLE 5.6 Gamma knife radiosurgery for miscellaneous neoplasms at the University of Pittsburgh (1987–2007)

Indications	Number of Patients Treated
Pineal region tumor	29
Craniopharyngioma	66
Hemangioblastoma	42
Chondrosarcoma	19
Chordoma	27
Hemangiopericytoma	33
Hemangioma	8
Myoepithelioma	1
Rhabdomyosarcoma	3
Esthesioneuroblastoma	4
Choroid plexus papilloma	11
Hypothalamic hamartoma	5
Lymphoma	11
Neurofibrosarcoma	1
Dysembryoplastic neuroepithelial tumors	2
Fibrohistiocytoma	5
Invasive skull base cancers	30
Others	21
Total	318

Innovation in Glioma Management

Advances in the management of primary brain tumors have steadily developed over the last 20 years despite a relatively small impact on survival. These significant advances include better neuroimaging, better cytoreductive efforts in patients who are eligible for such procedures, and enhanced and more aggressive radiation and chemotherapy trials. Despite these efforts, considerable controversy still exists as to the proper management of virtually all grades of gliomas. Our prior knowledge base has been clouded more recently by the recent realization that older patient survival statistics may be incorrect. Outcomes previously thought to be related to Grade II fibrillary astrocytomas instead may be biased by the likelihood that many such tumors would now be reclassified as oligodendrogliomas.[19] The recognition that many previously diagnosed astrocytomas are in fact 1P19Q-deleted oligodendrogliomas suggests that many historical studies related to fibrillary astrocytoma outcomes may be flawed.

We have worked with our radiation oncology and medical oncology colleagues to maximize the potential benefit of radiosurgery as an adjuvant treatment for patients with a wide variety of glial neoplasms. As might be suspected, the role of radiosurgery has been somewhat controversial in part as a result of differences in the training perspective of surgeons, radiation oncologists, and medical oncologists. We have chosen to amplify the potential value of radiation-related technologies for a very simple reason: in most glial tumors, radiation therapy is the mainstay of treatment and the sine qua non for survival. Especially for malignant glioma, the failure to deliver radiation therapy after diagnosis is tantamount to rapid progression and median survival of only a few months. Fractionated radiation therapy, now done with greater precision and less toxicity to tumor volumes defined by modern imaging, has also been refined during this same interval.

Juvenile Pilocytic Astrocytoma (Grade I Astrocytoma)

Predominantly tumors of childhood or young adults, juvenile pilocytic astrocytomas (JPAs) are tumors with more discrete borders, often have extensive contrast enhancement within them, and have a relatively distinct histopathology. When located in surgically accessible areas of the brain, resection is the mainstay of treatment. However, when located in critical areas of brain function, including the brainstem, optic pathways, or recurrent after resection of lobar tumors, JPAs are excellent tumors for radiosurgery. Especially in the childhood variant, with sharply defined imaging borders, we would prefer to use radiosurgery as a primary management strategy for unresectable tumors. The ability to give a radiobiologically more effective dose to a smaller volume in a single treatment session is very appealing (*Fig. 5.2*). Our initial results have been previously published.[26,29]

Currently, multicenter trials are evaluating potential upfront or adjuvant chemotherapy for JPAs. Until data further clarify the potential effectiveness of this treatment (which undoubtedly has a greater systemic toxicity), we think that the current data suggest radiosurgery is an effective management for smaller-volume JPAs. The dose must be delivered in

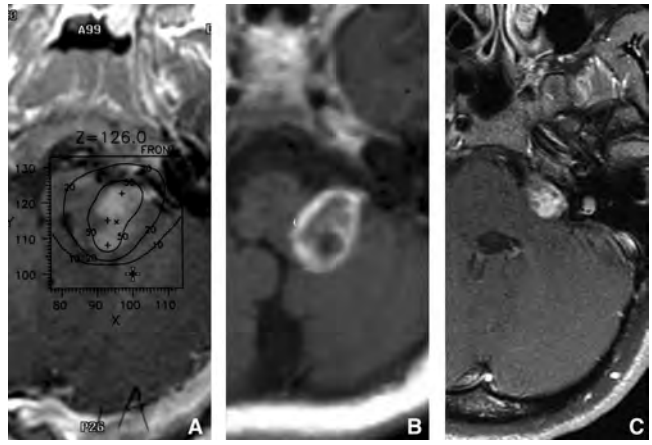

FIGURE 5.2. The initial radiosurgical MRI scan of a 4-year-old child with a residual pontine exophytic juvenile pilocytic astrocytoma (*A*). Six months later, the tumor shows central necrosis and slight enlargement (*B*). At 10 years, the tumor has regressed (*C*).

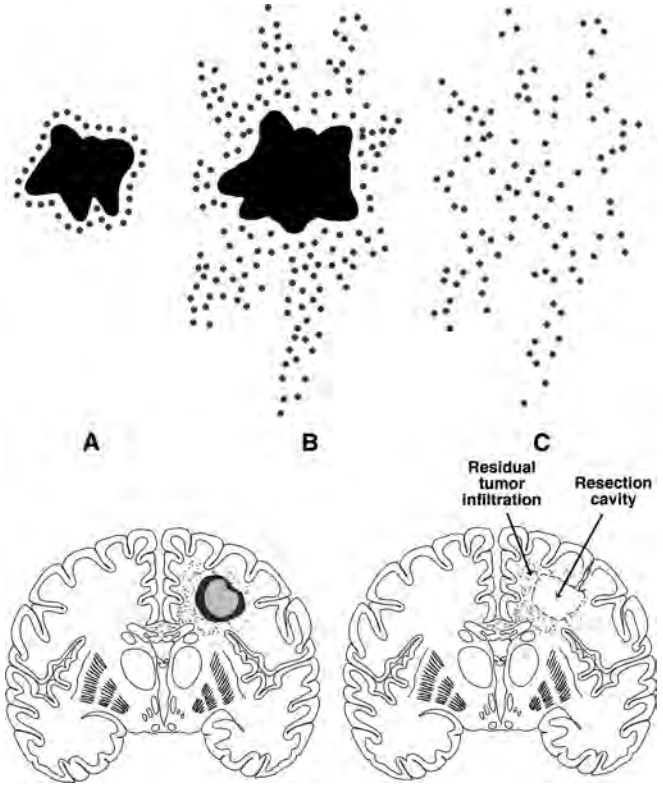

FIGURE 5.3. The spectrum of presentation of low-grade astrocytoma using the Daumas-Duport Classification (upper panel). Type 1 tumors (*A*) are generally JPAs but may include oligodendrogliomas. Type 2 tumors (*B*) are often astrocytomas Grade 2 to 4. Surgical resection alone leaves significant tumor burden behind (lower panel). Type 3 tumors (*C*) include gliomatosis cerebri for which no surgical options exist except biopsy.

a tightly conformal fashion with high selectivity (rapid dose falloff outside of the imaging-defined target volume).

Grade II Astrocytoma/Oligodendroglioma

No consensus exists among medical, surgical, or radiation oncologists as to the timing and role of intervention for a suspected Grade II astrocytoma. Observation, early biopsy, cytoreductive surgery, or radiation therapy have all been advocated for the management of such tumors. Most fibrillary astrocytomas have poorly defined borders with infiltrative edges. Such tumors are more commonly classified in the Daumas-Duport System as Type 2 or Type 3 (*Fig. 5.3*).[16] In certain patients with lobar or polar tumors, aggressive cytoreductive surgery may be beneficial. A tumor that is 30 to 60 g at the time of recognition contains approximately 3 to 6 $\times$ 10^{10} cells.[48,65] If a 90% resection is performed, there are 3 to 6 $\times$ 10^{9} cells. If a 99% resection is performed, there are 3 to 6 $\times$ 10^{8} cells remaining (*Table 5.4*). It is unrealistic to expect that such a remaining cell load (even after 99% resection) will not recur within a definable period of time. As we previously noted, a randomized, prospective trial designed to detect a 20% increase in survival benefit would require hundreds of patients and many years of follow-up[48] (*Table 5.7*).

We have used gamma knife radiosurgery in selected cases of biopsy-proven or postresection residual, small-volume Type 1 fibrillary astrocytomas and oligodendrogliomas.[28,30] The goal has been to reduce the potential long-term morbidity of wide-field fractionated external-beam radiation therapy. In tumors with imaging-defined evidence of grossly infiltrative extension into the deep white matter or deep white matter pathways, radiosurgery (as a focal surgical procedure) is unlikely to provide significant long-term tumor growth control. In those patients, other forms of adjuvant management must be considered, including fractionated radiation therapy and, for oligos, adjuvant chemotherapy. *Table 5.3* demonstrates our radiosurgical experience to date in the management of Grade II tumors at the University of Pittsburgh. For grossly infiltrative tumors without significant mass effect, we favor histological diagnosis followed by upfront radiation therapy. For a tumor that has a median life expectancy of 7 to 10 years, we do not think that observational strategies are indicated except in those rare patients in whom suspected tumors were seen incidentally on imaging studies and early diagnosis has unacceptable risks either by surgery or stereotactic biopsy technique. We have also used radiosurgery in the selective management of biopsy-proven gangliogliomas.

Malignant Gliomas

The current management strategies for patients with malignant tumors include early diagnosis, subtotal resection, radiation therapy, and consideration of various single or multicenter chemotherapy trials. We previously reviewed our experience in the use of adjuvant radiosurgery in malignant glioma and compared it with the Radiation Therapy Oncology Group

TABLE 5.7. To detect a 20% increased survival in patients who undergo gross total resection of a glial neoplasm compared with subtotal resection, a study would require long-term follow-up and high numbers of patients in each arm of the study

Median Survival of Historical Controls	Follow-up Years Required	No. of Patients Needed
7.5 years	7.5	587
	10	484
	12	434
	15	385
10.5 years	10.5	587
	14	484
	16.8	434
	21	385

(RTOG) survivals previously published.[38] In patients with RTOG recursive partitioning analysis Class III malignant gliomas,[25] we noted a median survival of 39 months with a 73% 2-year survival in comparison to a 35% 2-year survival in the same RTOG class. In patients with RTOG Class IV, we noted a 24% 2-year survival compared with a 15% 2-year survival in the RTOG cohort. In Class V tumors, we noted a 26% 2-year survival compared with a 6% 2-year survival rate in the RTOG study.

Certainly, selection bias may be in play in part because patients eligible for radiosurgery tend to have smaller-volume tumors. Gamma knife radiosurgery is used as a boost technique in these patients. The timing of radiosurgery application is as yet unresolved. Because of the length of time that it occasionally takes to complete intensity-modulated beam radiotherapy or IGRT radiation therapeutic planning for the treatment of a malignant glioma, some patients who present with deep-seated, relatively small-volume tumors undergo stereotactic biopsy first. Once a glioblastoma is confirmed, early upfront radiosurgery[75] can be performed, followed by external-beam fractionated radiation therapy (and often concurrent temozolomide) after planning is completed. The goal is to maximize the initial radiation benefit to such patients with malignant tumors with the recognition that almost all patients (to achieve meaningful survival) will need to have a combination of surgery, radiation therapy, and radiosurgery. Some may benefit from certain new chemotherapy trials.

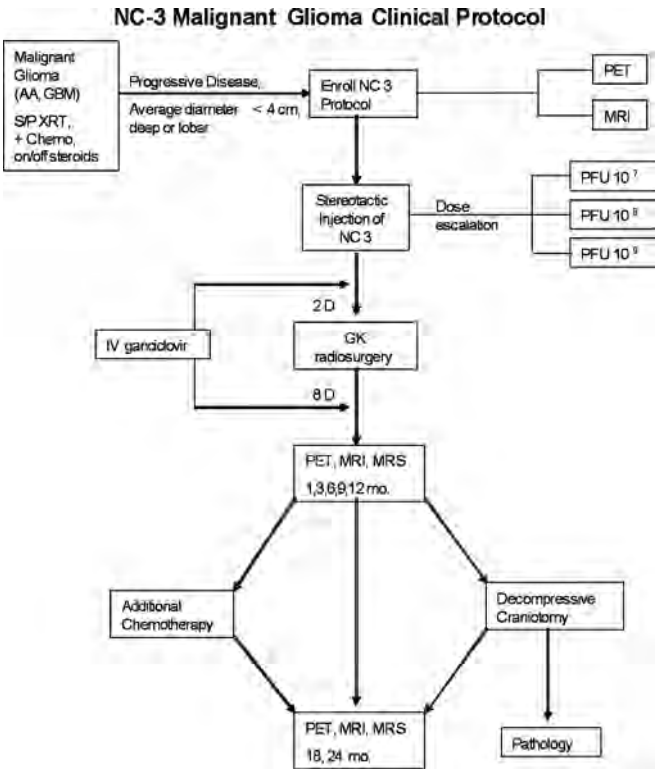

FIGURE 5.4. Proposed clinical trial of stereotactic placement of a polycistronic herpes simplex virus vector bearing four transgenes into recurrent malignant glioma followed by radiosurgery and ganciclovir therapy.

Herpes Simplex Virus-Mediated Boost Radiosurgery

For some years, our laboratory has been working in strong collaboration with our Department of Molecular Genetics and Biochemistry to introduce a clinical trial using a specially constructed nonreplicating herpes simplex virus-based viral vector, Nurel-C3.[58] Construction of this virus was based on four goals. The laboratory of Dr. Joseph Glorioso created a vector using a nonreplicating herpes simplex virus expressing thymidine kinase, ICP 0, tumor necrosis factor-alpha, and connexin-43. Connexin increases cell killing by bystander effect. Tumor necrosis factor-alpha is known to be a radiation sensitizer.[5,27,43] Our clinical proposal is based on the hypothesis that we can enhance tumor cell kill by combining an enhanced suicide gene therapy with an enhanced radiation killing effect. Work in several animal models have shown that when radiosurgery is combined with ganciclovir administration after the herpes simplex virus vector is delivered into the tumor, we can greatly increase the animal survival rate in both the C6 glioma and in the nude mouse model.[57,58] This project has been reviewed on several occasions by government oversight agencies and is currently pending final toxicology studies. Once an U.S. Food and Drug Administration Investigational New Drug is issued, we propose enrolling patients in this clinical trial (*Fig. 5.4*). Patients will have a staged multimodality approach; histological definition by surgery or biopsy, delivery of conventional fractionated radiation therapy, and systemic chemotherapy. For patients with eligible tumor volumes (average diameter smaller than 4 cm), stereotactic injection of nonreplicating herpes simplex virus will be followed by administration of ganciclovir. Three to 4 days later, boost gamma knife radiosurgery is performed. Because of the relatively poor outcomes of patients with glioma, we feel that new innovative treatment strategies are warranted. Having solved most oncopolitical concerns, this first human trial is anticipated in 2008.

Metastatic Cancer

The role of the neurosurgeon in the management of brain metastatic disease has been limited until the recent era of radiosurgery. In the United States, it is estimated that between 200,000 and 400,000 patients each year develop solitary or multiple brain metastasis from systemic cancer.[67] In times past, the reflex management for spread of cancer to the brain has been whole-brain fractionated external-beam radiation therapy, typically 30 to 35 Gy in 10 to 15 fractions. This treatment paradigm has been based on the concept of palliation of central nervous system disease and the prophylactic treatment of presumed micrometastatic disease beyond the resolution of conventional imaging. Since the development of high-resolution MRI, very

small brain metastasis in the range of 2 to 3 mm can frequently be recognized when an appropriate imaging protocol designed to detect such lesions is created. For example, during stereotactic gamma knife radiosurgical procedures for brain metastasis, we identified 20% or more brain metastases when double-dose contrast is administered followed by a 2-mm slice volume acquisition throughout the entire brain. Such a MRI technique significantly increases the detection of metastatic disease.[18] With this resolution, the argument for whole-head radiation therapy for subclinical brain metastases is no longer tenable.

Each year, perhaps 4000 to 5000 patients in the United States undergo craniotomy for resection of a brain metastasis. In contrast, hundreds of thousands of additional patients potentially are eligible for radiosurgical management. This paradigm shift has been promoted by a number of academic medical centers who have done excellent outcome studies relative to the alternative role of radiosurgery.[67] These studies have spanned almost 20 years during which hundreds of thousands of patients with metastatic cancer underwent radiosurgery. The role of radiosurgery has been defined in metastatic breast, lung, gastrointestinal, renal, and other rarer cancers.[20,32,36,51,66,69,70]

The majority of patients with brain metastatic disease achieve control by appropriately delivered radiosurgery. Long-term studies indicate that 80 to 90% will respond to radiosurgery. The cause of death of many patients with metastatic cancer has shifted from brain progression to systemic disease progression. Because radiosurgery is a single procedure that can treat one or more metastasis at the same time, patients do not need to interrupt their chemotherapy treatment programs, and patients are eligible for radiosurgery even if they are on systemic anticoagulation. The role of neurosurgeons has tremendously increased in the management of metastatic disease based on sheer numbers alone. The role of radiation oncology has shifted to team management using radiosurgery.

As might be expected, this has led to some consternation among various oncologic circles because whole-brain radiation therapy as a primary management of central nervous system cancer has long been ingrained in the teaching of radiation oncology. Its role is based more on the concept of brain tolerance than radiobiological effectiveness. Many studies have shown the significant advantage of adding radiosurgery to whole-brain radiation therapy.[1,12,40] More recent studies have shown the potential value of using radiosurgery alone for multiple brain metastasis.[7,31,45,50] Because radiosurgery can be repeated as needed over the course of a patient's remaining life, multiple procedures over the course of months to years may be necessary if new disease develops.

One of the primary outcomes in the use of radiosurgery has been the reduction of the long-term risk of delayed cognitive disorders, a long-term outcome of whole-brain radiation, which increases in frequency in those patients who survive more than 1 year. After administration of whole-brain radiation therapy alone, median survivals of metastatic brain cancer often were in the range of 3 to 7 months depending on the type of cancer. Delayed white matter changes and associated cognitive dysfunction was recognized only in those patients who had longer survivals, usually because of good systemic disease control. For selected cases with favorable prognostic features, for example, a solitary brain metastasis from nonsmall lung cancer in a patient with no evidence of active systemic disease elsewhere, median survival after radiosurgery may be extended into multiple years.

Based on the sheer number of metastatic disease to the brain, there are probably insufficient numbers of neurosurgeons performing radiosurgery or even being trained to meet

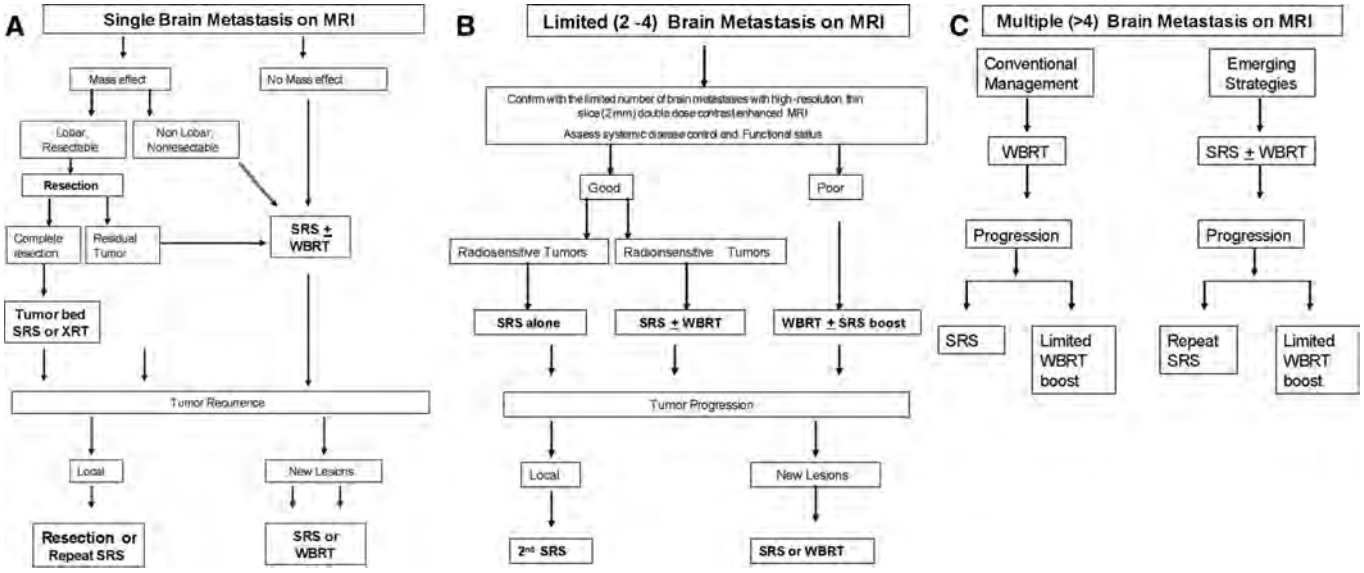

FIGURE 5.5. *A–C,* A proposed schema for therapeutic options in the management of metastatic brain cancers.

the potential clinical demand. Currently, most radiosurgical centers act in a collaborative and collegial method. They rely on the talents of neurosurgeons who partner with radiation oncologists and medical physicists. Over the last 10 years, the growing use of radiosurgery has percolated through national and international meetings and has been the subject of Levels 1,[1,3,12,40] 2,[4,22,72] and 3[31,45,50,66,69,70] evidence-based medicine reports. A paradigm for the role of radiosurgery is shown in *Figure 5.5*.

More recently, the potential role of radiosurgery for the tumor bed of patients who have undergone craniotomy and resection of a brain metastasis has been explored.[59,73] The goal of this paradigm remains the same, i.e., reduction in the risk of delayed cognitive dysfunction while maintaining or improving local control rates. To date, no Level 1 evidence (randomized, prospective trials) have been performed to assess the potential benefit of tumor bed radiosurgery versus conventional whole-brain radiation therapy after craniotomy. Such a study may be necessary to define the eventual place of tumor bed radiosurgery. Hopefully that study will address many oncopolitical issues such as efficiency of care, ability to repeat radiosurgery, potential crossover therapy if whole-brain radiation therapy is ultimately required, cost-effectiveness, quality of life, and cause of death. No single diagnosis has had a greater impact on the potential value and role of radiosurgery nor encouraged its widespread use than has radiosurgery for metastatic disease. Effective dose technique and volume relationships to dose are reasonably well worked out. For tumors thought to be radiation-resistant such as melanoma and renal carcinoma, stereotactic radiosurgery is particularly valuable. It can largely replace whole-brain radiation therapy as the initial preferred management for patients with one or more brain metastases. Long-term adverse radiation risk rates are related to the size and volume of the tumors. Certain tumors, especially melanoma and renal cell, are still prone to intratumoral bleeding, which may ultimately require additional management strategies, including craniotomy if the tumor is located in a surgically approachable region of the brain. *Table 5.5* shows our 20-year radiosurgery experience by primary cancer diagnosis. We continue to advocate the role of radiosurgery as a primary management for metastatic brain tumors.

It is likely that the oncopolitical issues associated with radiosurgery will soon fade. For most current radiation oncology practitioners, the partnership with neurosurgery has provided a strong professional bond. The continued role of the neurosurgeon can be assured, but only if they are actively involved in all aspects of the procedure. The neurosurgeon's role in the realm of radiosurgery includes patient selection, description of alternative strategies, stereotactic head frame application, imaging, dose planning, and radiosurgical treatment delivery and concludes with frame removal. The role of the neurosurgeon is less clear when linear accelerator technologies and multiple treatment sessions (previously called fractionation) are used in linear accelerator-based strategies.

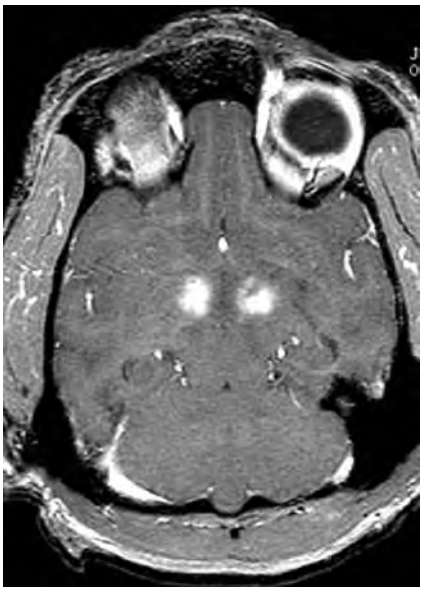

FIGURE 5.6. Ventrolateral hypothalamotomy using radiosurgery for an obese monkey model (contrast-enhanced MRI scan).

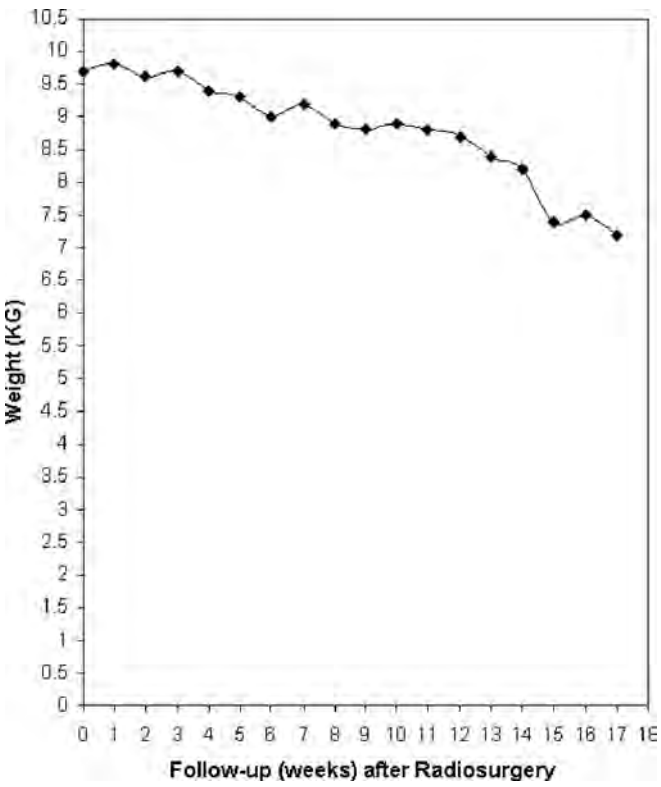

FIGURE 5.7. The weight loss pattern in an obese monkey after ventrolateral radiosurgical hypothalamotomy.

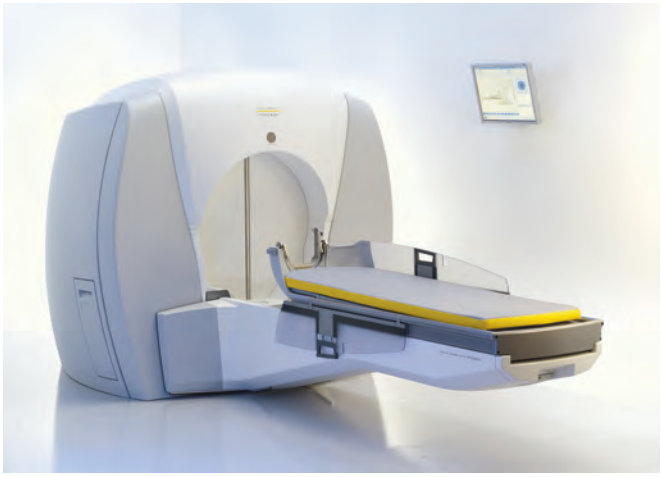

FIGURE 5.8. The latest generation gamma knife, Perfexion, uses 192 cobalt-generated photon beams and completely robotic positioning (Courtesy of A. B. Elekta).

Obesity

Although human obesity is a rampant epidemic, especially in the United States,[1] it certainly does not present a cancer-associated (oncopolitical) concern. Nonetheless, the potential role of the neurosurgeon in the management of a condition such as morbid obesity is sure to raise turf or political issues. Human obesity is a major cause [1]of death in the United States related to strain on the cardiovascular system and development of diabetes mellitus. At the present time, there is only one truly effective procedure, variations in gastric bypass surgery. All such procedures have significant medical and surgical risks, including pulmonary embolus and death. Although effective in creating significant weight loss, the procedure requires additional lifestyle changes as well. To evaluate the possible role of functional radiosurgery in the management of obesity, we created an experimental model using obese monkeys. Obese monkeys can be created by a diet high in foods such as potato chips.

We have known for many years from animal models, and an occasional human case, that destructive lesions of the ventrolateral hypothalamus can lead to resetting of brain glucose receptors, changes in metabolic rate, and weight loss. We wanted to create a primate model and perform radiosurgical ventrolateral hypothalamotomy to treat this complex disorder. The eventual goal was to assess whether such a procedure in humans might lead to sustained weight loss. If so, radiosurgical hypothalamotomy might replace more morbid operations such as gastric bypass surgery.

Obese cynomolgus or rhesus monkeys underwent stereotactic head frame application and identification of the ventrolateral nucleus of the hypothalamus. Because of the small size of the monkey brain, identification of this target required a high-resolution MRI scan fused with the stereotactic images before target selection and eventual radiosurgery. *Figure 5.6* shows a lesion in the ventrolateral hypothalamus of the monkey. *Figure 5.7* shows a weight loss pattern in kilograms after radiosurgery. This initial experience suggests the feasibility of hypothalamotomy in adults.

For three decades, stereotactic radiosurgery has been used for movement disorders and chronic pain. Lesions of the

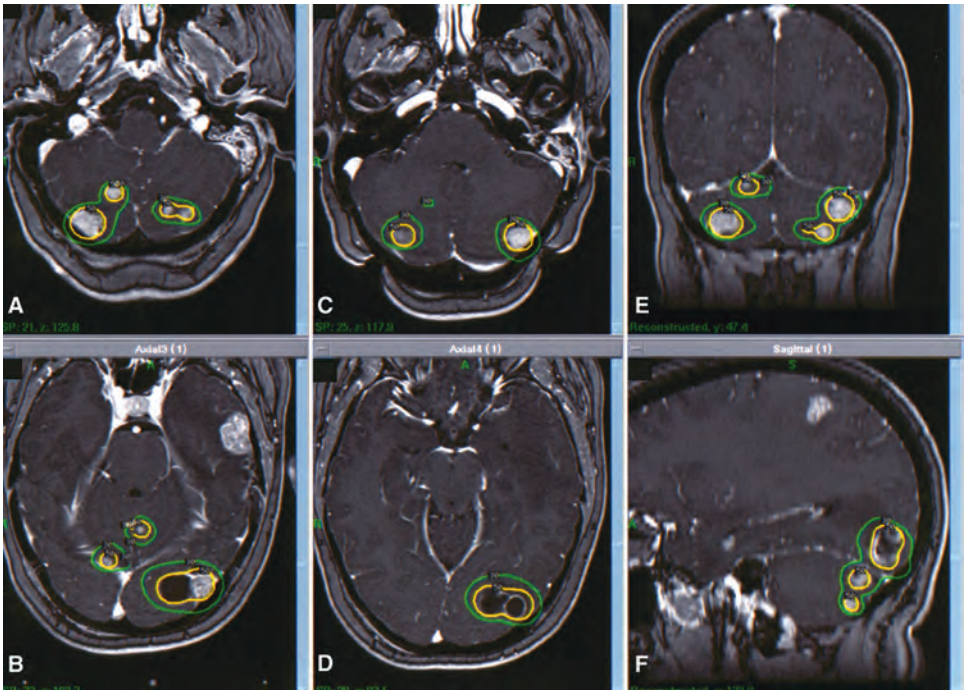

FIGURE 5.9. Patient with scattered multiple brain metastases treated using the Perfexion model gamma knife.

ventrolateral nucleus of the thalamus typically require 120 to 140 Gy using a 4-mm collimator. This results in the development of a predictable 5- to 6-mm lesion within 2 to 6 months. This procedure has been particularly valuable for patients with essential tremor or for patients with Parkinson's disease ineligible for deep brain stimulation. We have been reluctant to perform pallidal radiosurgery because of the closeness of the optic apparatus. However, with current technologies, it is possible to create a subnecrotic radiation lesion in the hypothalamus and still spare the optic tract and apparatus. We believe that a cautious, prospective Phase I trial is feasible to be able to test the hypothesis that a ventrolateral hypothalamotomy can lead to weight loss. In summary, this area of using radiosurgery to treat obesity is still controversial and under investigation and therefore is not ready for prime time.

Creation of the New Gamma Knife (LGK Perfexion)

One of the great benefits of multidisciplinary (nonpolitical) medicine has been the ability to create teams of specialists who come from different training backgrounds and who can work together to pioneer new technologies. The goal of this project was to identify those necessary but improvable features of prior generation gamma knives to create a new model. This exciting venture led to an example of how to resolve oncopolitical issues. A dialogue was formed within the team and brainstorming meetings were held in various countries, especially Sweden.

From these discussions, a new product emerged (Perfexion AB Elekta, Stockholm, Sweden) to take gamma knife technology to the next level (*Fig. 5.8*). The development goals of this product included expanding potential indications and range of anatomic targets while maintaining the beauty and simplicity of the original Leksell concept, increasing patient efficiency and patient flow, and improving the dose profile and dose delivery. Initial clinical trials were completed under the direction of Professor Jean Regis at Marseille, where the first clinical Perfexion was placed.[6,61] Additional units have now been placed in London and began operation in the United States in the summer of 2007. LGK Perfexion was installed at the University of Pittsburgh medical center in September 2007. The Perfexion unit is especially valuable in the treatment of multiple brain metastases, because patients do not need to be repositioned, and the risk of collision for laterally, inferior or posterior lesions is resolved using the expanded aperture of the gamma knife (*Fig. 5.9*). Additional technological development is going to be required to facilitate treatment in the head and neck and upper cervical spine region. Studies will no doubt be forthcoming from a variety of institutions, especially those that have been able to pursue innovation and push oncopolitical concerns to the back burner.

CONCLUSION

New technologies, changes in treatment paradigms, and the breaking down of turf barriers all have the potential for startling advances in medical care. No single specialty has the knowledge or clinical base to practice alone. Innovation occasionally will collide with oncopolitical issues, but it is likely that innovation, buttressed by experience and results, will win.

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