In This Issue

GLIOBLASTOMA
Of all the primary brain tumors, astrocytomas are the most frequently occurring. They are divided into four classes, I – IV, with Grade I being very slow growing and Grade IV being very aggressive and malignant. Oftentimes, lower-grade astrocytomas are diagnosed by their scan appearance and then observed over time until the scan changes or the patient develops symptoms. Patients with Grade IV astrocytomas are almost always symptomatic (i.e. these tumors are rarely found incidentally), and unfortunately these are the most commonly encountered tumors in this group.

Another name for Grade IV astrocytoma is glioblastoma, and sometimes the term glioblastoma multiforme (GBM) is used. Approximately 12,000 cases of GBM are diagnosed each year in the United States. Even though improvements have been made in chemotherapy, radiotherapy and surgical intervention, the prognosis for glioblastomas is relatively poor. The survival rate of GBM remains among the most unsatisfactory of all cancers, with median survival less than 12 months in most studies and a five-year survival rate of approximately 3.3 percent for patients age 40-75 years. Central Tumor Registry Data indicates that 62 percent of patients with GBM expire within two years of diagnosis.

Causes of Glioblastoma
No proven risk factors directly related to glioma have emerged from years of data accumulation. Heredity does play a role in some cancers, but no specific genetic factors have been found involving primary brain tumors. An elevated risk in the incidence of glioblastoma multiforme has been found within the context of the Cancer Family Syndrome, which is generally associated with leukemia, soft tissue sarcomas and breast cancer. In some families in which cancer is prevalent the tendency to develop anaplastic astrocytoma is a dominantly inherited trait. Malignant astrocytomas (glioblastomas), however, seldom occur as inheritable disease except when they are a part of the
constellation of neoplasms observed in the Cancer Family Syndrome. Age (above 55 years) seems to be a consistent factor in glioblastoma multiforme, with a greater incidence as age increases. Long-term exposure to various carcinogens, including heavy metals, aromatic chemicals and agents such as vinyl chloride, has been implicated as an increased risk for glioma. Diets high in N-nitroso compounds (found in cured meats) also are linked to an increased risk of glioma. Microwave radiation, as found in cellular telephones or certain electromagnetic fields, has not been associated with tumors of the Central Nervous System, including GBM.

Clinical Presentation
Two kinds of neurological symptoms, general and focal, are associated with intracranial tumors. General symptoms are related to increased intracranial pressure and include vomiting, nausea and headaches. Focal neurological symptoms can include aphasia, hemiparesis or visual field loss. Approximately 50 percent of patients with glioma present with headaches. They may have unilateral characteristics of a throbbing nature.

Patients with primary brain tumors such as GBM may also present with a seizure and approximately 15-25 percent of patients with GBM have seizures. Thirty-50 percent present with hemiparesis and 40-60 percent demonstrate mental status abnormalities at the time of diagnosis.

Diagnosis and Prognostic Factors
Neuroimaging is the initial diagnostic modality for the assessment of GBM. Contrast enhanced magnetic resonance imaging is currently the most used tool. The appearance of GBM is characteristically irregular, with enhancing margins and intrallesional areas of hyperintensity alternating with areas of hypointensity (necrosis). The lesions are usually located in deep white matter, with fascicular extensions, seen best on T2 and FLAIR images. When neuroimaging and neurologic examination suggest GBM, tissue diagnosis is achieved either through biopsy or cytoreductive surgery. Cytoreductive surgery, the most vigorous removal of abnormal tissue that is possible in the context of preservation of neurological function, has been associated with the best long-term outcome. Currently, craniotomy using stereotactic navigation is a commonly used technique which allows for more accurate surgical planning and tumor removal while minimizing surgical morbidity and mortality.

Histopathologic characteristics of glioblastoma include cellular pleomorphism, perivascular proliferation and necrosis.

Prognostic factors of GBM include histologic diagnosis, age, performance status (assessed by the Karnofsky Performance Scale), type and duration of symptoms and extent of surgical resection. Younger patients under 50 who present with a higher functional status do best and can have a median survival of 59 months, while patients older than 50 who are less functional and have an abnormal mental status prior to surgery have a much lower median survival of only approximately five months.

Management of the Newly Diagnosed Glioblastoma Multiforme
Because glioblastomas infiltrate the surrounding normal tissue often by many centimeters from the focus of the primary lesion, radiotherapy is necessary after surgery. Brain tissue is not very tolerant of high radiation doses, and this becomes the limiting factor in providing complete cure or even control of tumor spread. Doses of up to 60 Gy have been used, spread out over approximately 30 treatment sessions. Although radiotherapy rarely cures glioblastoma, studies show that the median survival of patients receiving radiotherapy is twice that
of those who are not radiated. Patients treated with radiation have a two-year survival of 10 percent.

Temodar (temozolomide) is an oral alkylating compound shown to have antitumor activity against GBM. Temodar can be given orally and has the advantage of being generally well tolerated, with only 14 percent of patients developing hematologic toxicity. Recent trials demonstrate conclusively that the combination of radiotherapy with concurrent Temodar chemotherapy significantly improves survival compared to radiotherapy alone. The addition of Temodar increased median survival from 12.1 months to 14.6 months and nearly tripled the two-year survival from 10 to 26 percent. From these results, the regimen of postoperative radiation therapy and Temodar has become the standard routine for patients with newly diagnosed GBM.

Interstitial chemotherapy in newly diagnosed GBMs has also shown some clinical benefit. The implantable chemotherapy wafers, also known as Gliadel, have demonstrated an approximate two-month extension of survival in addition to the benefits of radiation and surgical debulking alone.

Treatment for Recurrent Glioblastoma Multiforme

For patients with reasonable neurologic status who have survived more than about six months from initial treatment and show evidence of recurrent disease, further surgical and adjuvant therapy may be considered. This may include further surgical debulking for symptoms of mass effect such as headaches, nausea or vomiting. Gliadel wafer implantation can be considered along with this second surgical tumor resection and may add approximately two months to survival, although there is an increased risk of wound breakdown and seizures with Gliadel wafers. If Temodar was previously discontinued in a patient with recurrence, it can be reinstituted and some studies have shown an additional 7-13 months of median overall survival, although most studies have yielded much worse results. Stereotactic radiosurgery, usually not considered in the initial treatment for GBM, can be considered for small focal recurrences, less than 3.5 cm in size. However, the results of this treatment modality are more anecdotal than statistically significant. Avastin (bevacizumab) is another chemotherapy agent which can be considered for GBM recurrence. Avastin inhibits blood vessel formation and therefore is classified as an angiogenesis inhibitor. It has been associated with approximately a 60 percent response rate in recurrent GBM, with a six-month survival rate of about 43 percent, whereas the six-month survival rate for patients taking Temodar for recurrent GBM is only 21 percent.

Metastatic Brain Tumors

Incidence and Epidemiology

The leading sources of metastatic brain tumors are lung (44 percent), breast (12 percent), melanoma (10 percent) and gastrointestinal system (six percent). Metastatic tumors to the brain occur in up to 200,000 people per year and represent a significant source of neurological debilitation and premature death. Eighty percent of brain metastases occur in the cerebral hemispheres, 15 percent in the cerebellum and five percent in the brainstem.

Treatment of Brain Metastases

As with GBM, treatment of brain metastases includes surgery, radiation therapy and chemotherapy to achieve maximum quality of life and prolonged survival. The options for treatment of metastatic brain tumors depend on the extent of CNS involvement, surgical accessibility of the lesion(s), the presence or absence of systemic disease, the patient’s overall condition, his/her neurologic condition and the radiobiologic and chemotherapeutic susceptibility of the tumor. Symptoms of brain metastasis can be treated with medications such as anticonvulsants, corticosteroids and analgesics. Recommendations for the definitive treatment of initial or recurrent brain metastases include a combination of surgery and whole brain radiation therapy and/or stereotactic radiosurgery. Surgical resection of a single or surgically accessible multiple lesions results in an increase in median survival averaging 8-10 months, along with relieving or stabilizing neurologic symptoms. However, without adjuvant therapy, the probability of local recurrence is quite high (50-60 percent). In patients with a single intracranial metastasis, the addition of whole brain radiation therapy to surgical resection reduces overall recurrence rate by 50 percent, recurrence at the original site by 36 percent and death from neurologic causes by 30 percent. However, the addition of whole brain radiation therapy to surgery has not been shown to significantly improve overall survival or increase the length of time the patients remain functionally independent.

While whole brain radiation therapy alone results in a much lower survival rate than surgery plus whole brain radiation, there is a subgroup of patients who may be considered for treatment only with whole brain radiation. This protocol is generally applied when a patient has a surgically inaccessible tumor, multiple brain metastases (more than five tumors), poor neurologic function or disseminated systemic disease with a poor overall prognosis. Unfortunately, whole brain radiation therapy alone is not as successful in reversing neurological
symptoms (i.e., by reducing mass effect) as is surgery plus radiation and chemotherapy. Seventy-eight percent of patients with radiation alone had either no improvement or actual progression of neurologic symptoms at one month after whole brain radiation.

There is also evidence of radiation-induced dementia and decreased quality of life after whole brain radiation. Because of these drawbacks regarding whole brain radiation, the focal treatment of lesions with stereotactic radiosurgery has been advocated. Stereotactic radiosurgery applies high-dose, highly conformed radiation to individual lesions in a single session or a few fractionated treatments. Local disease control rates generally average about 75 percent for one or more brain metastases. This treatment modality is generally limited to those patients with five or fewer intracranial metastases. Control of “radioresistant” tumors such as renal cell carcinoma and melanoma can be expected to be less than 50 percent. Potential complications include edema, seizures and radiation necrosis. While there is no significant difference in survival among patients treated with stereotactic radiosurgery, with or without the addition of whole brain radiation, there is evidence for better CNS control of disease with whole brain radiation therapy plus stereotactic radiosurgery vs. whole brain radiation alone. Also, the addition of whole brain radiation to stereotactic radiosurgery gives better salvage results and reduced incidence of brain tumor recurrence at one year, although the incidence of radiation necrosis is increased.

In summary, the use of whole brain radiation and stereotactic radiosurgery did not improve survival in patients with 1-4 brain metastases compared with stereotactic radiosurgery alone, but the addition of whole brain radiation to stereotactic radiosurgery significantly improved lesion control rates. Further, the need for salvage treatment was significantly greater for patients who received stereotactic radiosurgery alone as compared to those who had also received whole brain radiation.

**SPINE METASTASES**
Metastatic bone pain is the most common pain syndrome encountered in cancer patients. If the metastases involve the spine, besides the disabling pain, there can be destruction of the vertebral body leading to spinal instability, compression of the spinal cord and/or nerve roots with eventual neurological dysfunction and paralysis. Both early detection and appropriate intervention are essential to minimize the sequelae of spinal metastases and maximize patient function and quality of life. The goals of treatment for spinal metastatic disease are pain control, preservation of spinal stability and the maintenance of sphincter control and ability to ambulate.

The most common sources of spine metastases are from lung, breast, prostate and kidney. Pain is the first symptom in 95 percent of patients and may be focal or radicular. If spinal cord compression occurs, weakness, numbness, and bowel and urinary difficulties can follow. Seventy-six percent of patients have weakness by the time of diagnosis and 15 percent are paraplegic on initial presentation. Metastatic disease of the spine is best diagnosed by MRI scans with contrast. In patients with pacemakers or other implanted electrical devices, CT scans with or without myelography are necessary to guide therapeutic interventions.

The greater the neurologic deficit when treatment is initiated, the worse are the chances for recovery of lost function. Less than five percent of patients presenting with paraplegia can ambulate after aggressive treatment. The median time from
onset of symptoms to diagnosis is two months. In patients who present with significant neurological deficits such as paraplegia, a 24-hour course of high-dose intravenous steroids may help in determining whether surgical intervention should be considered; if there is no improvement in strength after 24 hours, it is unlikely that surgical intervention will help regain significant motor function. However, the age of the patient should also be considered in that younger patients with severe spinal cord progression may respond better to aggressive surgical decompression.

If the neurologic deficits are not significant, then radiation therapy is quite helpful in controlling pain with significant improvement within the first week of radiation therapy. If weakness or surgically significant spinal deformity is present, it is best to intervene surgically and allow the skin to heal for approximately two weeks before beginning radiation therapy. There is a theoretical risk of radiation-induced edema causing or accelerating neurologic deterioration. Symptoms of this can usually be controlled by the use of steroids; in general, significant deterioration is more likely because of tumor progression. As of yet, no chemotherapy has been found to be as useful as surgery and radiation therapy in the treatment of spinal metastases.

Finally, in patients who are elderly and frail or who already have profound neurological deficits, or in those who have a limited life expectancy (< six months or so), often treatment with comfort measures and/or radiation without surgery is more humane and avoids the increased pain post-operatively, along with the morbidity and rather poor results of surgery in the face of poor nutrition, low performance status and depression.

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Intracranial Stereotactic Radiosurgery

By Samuel McGrath, M.D.

Originally introduced in 1951, stereotactic radiosurgery (SRS) is a radiation therapy delivery technique in which multiple beams converge onto an intracranial target, depositing a high dose of localized irradiation within a small volume. Radiation beams are delivered either via a Gamma Knife, a dedicated radiosurgical unit using gamma radiation from multiple cobalt sources or a conventional medical linear accelerator specially adapted with circular collimators of varying diameter as employed here at Memorial Hospital of South Bend. Current applications include treatment of brain metastases, acoustic neuromas, arteriovenous malformations, pituitary adenomas, recurrent gliomas and even trigeminal neuralgia.

On the date of the procedure, a stereotactic frame is affixed to the patient by a neurosurgeon under local anesthesia and will remain in place until completion of the radiation treatment. Frame placement is a critical step in this process, as it provides a relationship between the patient’s intracranial anatomy and the coordinate system that will be employed for target localization. Thereafter, a CT scan of the brain is obtained and subsequently fused with a thin slice MRI for treatment planning purposes. The target and normal surrounding critical tissue structures are contoured by the radiation oncologist and neurosurgeon. A treatment plan is generated and subjected to exhaustive quality assurance prior to delivery. Treatment generally takes less than an hour, after which time the frame is removed and the patient is discharged home.

Eligibility for radiosurgical treatment is predicated upon the geometry of the target lesion. This treatment is best suited for spherical lesions under four cm in size. Selection of radiation dose is contingent upon the size of the lesion and biology of the tumor. Larger targets result in irradiation of more normal brain tissue, thus a lower dose is utilized. Treatment can be administered as either initial therapy or as a salvage option in the setting of prior conventionally fractionated whole brain radiation treatment.

For those eligible for radiosurgical treatment, the advantages are myriad. Dose gradients at the edge of the treatment volume are steep, allowing for a rapid fall off in dose. Radiosurgery is extremely accurate as well, with dose being deposited with submillimeter precision. This optimally spares the normal surrounding neurologic tissue, resulting in less acute and chronic toxicity. This treatment approach circumvents the need for surgical removal of the lesion, offering up a much less invasive therapeutic alternative. Radiosurgery is administered in a single fraction, replacing a standard three to six week treatment course, allowing patients the option to start additional treatment such as chemotherapy sooner. Finally, the single large dose of radiation is advantageous radiobiologically, allowing less tumor cells to survive the initial radiation insult and in turn increasing the efficacy of treatment.

Memorial Regional Cancer Center is pleased to offer the region’s only intracranial stereotactic radiosurgical program. Working in close collaboration with the neurosurgeons from North Central Neurosurgery, we are able to treat all of the aforementioned disease entities safely and effectively.

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Brain tumors are problematic in part because of their location. They do not have to become very big before they begin to disrupt an essential bodily system. Because of the central nervous system’s sensitivity, the body has built multiple methods to protect the brain from potentially harmful intruders. One of the strongest of these protective mechanisms is the “blood brain barrier.” It allows only glucose, oxygen, electrolytes and other small molecules to travel back and forth. This system that protects the central nervous system also seems to work to protect brain tumors from chemotherapy. There is some disruption in that barrier in the presence of malignancy, but one of the bigger difficulties in treating brain tumors is delivering the drug to the tumor cells. The families of drugs that are lipid soluble can transverse that barrier but the great preponderance of chemotherapy that we have available today is water soluble, not lipid soluble.

The stage of a brain tumor does not matter in the same way that the stage of a solid tumor arising in other organs do. It is often part of a patient’s final event for a cancer that arose elsewhere in the body to spread to the brain. It is then that the metastases to the brain proves fatal.

Primary brain tumors do not have to spread to another organ to be fatal; the grade of the malignancy carries more significance than the stage. As noted in Dr. Langheinrich’s article, the highest grade, most malignant and most common astrocytoma is designated glioblastoma multiforme (GBM). Standard therapy has been surgical resection followed by radiation. In 2005, a study compared a. surgical resection followed by radiation to b. surgical resection followed by radiation in conjunction with the oral (lipid soluble) agent temozolomide (Temodar), followed by one year of temozolomide. For the group that was treated by the standard method, survival at two years was 10 percent. For the group treated with temozolomide, survival at two years was 26 percent. While 26 percent survival at two years is not a victory, it does represent a significant improvement. As is often the case, an answer to one question raises a new set of questions. Is the temozolomide in conjunction with the radiation the most important part of the treatment? If one year of temozolomide after radiation is a good thing, is two years of temozolomide even better? These questions are currently under review.

The vascular endothelial growth factor receptor blocker bevacizumab (Avastin) has demonstrated true utility in GBM. It both improves quality and extends the life of the patient. This is somewhat surprising, as it is a large protein molecule and cannot get through the blood brain barrier to directly interact with the tumor cells. It has been pointed out that there is a disruption of the blood brain barrier in the presence of tumor. In fact, the vascular endothelium and the blood brain barrier appear to be repaired in the area where tumors that have been treated with bevacizumab are located. A tumor in the brain incites edema in the surrounding area. This edema disrupts normal brain function and magnifies the effect of the tumor. It is quite valuable to shrink the edema itself. Even with no shrinkage of the tumor, it decreases the effect of the malignancy on the patient. It has been speculated that all of bevacizumab’s benefits are mediated by its potent activity against swelling.

Vaccines against cancer remain an enticing therapy. Some activity as therapy, not merely as a preventative, has been demonstrated in melanoma. Vaccines against breast cancer, colon cancer, lung and prostate cancer are being developed now. Studies are currently ongoing utilizing vaccines against glioblastoma. The patient’s own cells are collected and are “trained” by being exposed to proteins that are found preferentially on glioblastoma cells. This is a difficult area because every protein found on any cancer cell is a protein that is a normal constituent of some normal cell at some normal place and time. It is important that the cells do not end up “trained” to attack the normal cells of the body. Once the lymphocytes or “dendritic cells” are trained to recognize the selected GBM target, the patient receives some standard therapy. The vaccine consisting of the dendritic cells is then injected back into the patient. Part of the reason that dendritic cell vaccine is of special interest in GBM is because these dendritic cells can, of their own volition, traverse the blood brain barrier to get directly to the target GBM cells.

I hope that this has explained to you some of the interesting developments in the treatment of this terrible disease and why I remain cautiously optimistic for the future. I further hope you can now share some of the excitement that we in the field feel as new research goes forward.

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