Oncodiagnosis Panel: 2002

Adult Central Nervous System Neoplasms

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Introduction

An estimated 17,000 new cases of primary central nervous system (CNS) tumors will be diagnosed in the United States in 2002 (1). The number of related deaths is projected to be 13,100. These numbers represent a small proportion of the total number of new cancer cases and cancer deaths; however, because of the diversity and complexity of CNS tumors, a multidisciplinary approach is required for their diagnosis and treatment. Treatment options for the different tumors vary widely from observation to aggressive combinations of surgery, radiation therapy, and chemotherapy.

Because of the complexity of as well as the controversy surrounding management issues, adult CNS neoplasms were the featured topic of the Oncodiagnosis Panel at the 2002 scientific assembly of the Radiological Society of North America. Experts on neuro-oncology (T.F.C.), neuro–radiation oncology (G.S.B.), diagnostic neuroradiology (J.T.W.), and neurosurgery (M.W.M.) were presented adult CNS neoplasm cases for discussion. The ensuing article outlines each case as presented in the Oncodiagnosis Panel followed by questions posed to the experts and their commentaries given in response. The CNS neoplasms discussed include oligodendroglioma, multiple brain metastases from non-small cell lung cancer, glioblastoma multiforme, and meningioma of the optic nerve.

Abbreviations: EORTC = European Organization for Research and Treatment of Cancer, NCCTG = North Central Cancer Treatment Group, RTOG = Radiation Therapy Oncology Group

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Case 1
A 40-year-old woman presented with new onset of right-sided headaches and photophobia. Findings from a detailed neurologic examination were negative except for an essential tremor of the upper extremities. Magnetic resonance (MR) imaging was performed and revealed a lesion involving the left posterior frontal operculum and insula (Fig 1).

Diagnostic Radiologist’s View

*Question: What Is the Differential Diagnosis?*—Differential diagnostic considerations for this nonenhancing well-circumscribed mass within the left frontal lobe would include low-grade astrocytoma, oligodendroglioma, ganglioglioma, or dysembryoplastic tumor (DNET). The lack of contrast enhancement and well-circumscribed appearance would favor a lower grade lesion (2).

Neuro-oncologist’s View

*Question: How Should This Patient Be Further Managed, with Observation, Further Imaging Studies, Biopsy, or Resection?*—The images show a well-circumscribed, non–contrast-enhancing lesion in the left frontal region without perilesional edema. The patient’s symptoms, as described, likely are not related to the lesion seen in the MR images and, therefore, are likely incidental to the MR imaging findings. Because these are the first images documenting this lesion, the rate of change is unknown. There are no data to support early intervention being better than watchful waiting for this lesion that is likely a low-grade glioma (3,4). Therefore, the patient should be engaged in a full discussion about the risks and benefits of intervention versus watchful waiting. If intervention were to be considered, a tissue diagnosis should be strongly considered. If a surgical approach were used, considerations of biopsy versus attempt at resection should be discussed. Although some data support an improved prognosis in patients who undergo a gross total resection of a low-grade glioma (5–8), there does
not appear to be an advantage to performing a subtotal resection versus a biopsy (other than a subtotal resection possibly ensuring more effective sampling) (9). The patient is likely right-handed and likely has significant representation of language in the left hemisphere. An attempt at resection might put the patient at risk for permanent language loss, whereas without surgical resection she might be highly functional. One other consideration in favor of surgery would be to obtain a histologic diagnosis. As many as 30% of anaplastic astrocytomas do not have imaging contrast enhancement (9,10). Because the therapy for anaplastic astrocytoma can be very different than that for a low-grade astrocytoma, patients should give strong consideration to obtaining a tissue diagnosis. As many as 30% of anaplastic astrocytomas do not have imaging contrast enhancement (9,10). Because the therapy for anaplastic astrocytoma can be very different than that for a low-grade astrocytoma, patients should give strong consideration to obtaining a tissue diagnosis. 

After a thorough discussion with a neuro-oncologist and neurosurgeon, the patient elected to proceed with observation with follow-up on an annual basis. At a follow-up visit 3 years after initial diagnosis, the patient noted an approximate 12-month history of right-sided “spells.” Electroencephalography was performed at her local medical facility, and she was found to have no epileptiform activity. Results of a detailed neurologic examination were negative, except for mild drooping of the right lower face. MR imaging was performed (Fig 2).

**Neuro-oncologist’s View**

**Question: How Should This Patient Be Further Managed, with Observation, Further Imaging Studies, Biopsy, or Resection?**

—Three things have happened with this patient during watchful waiting: (a) MR imaging has shown evidence of growth, (b) the patient is exhibiting new symptoms referable to the lesion, and (c) the patient has neurologic signs referable to the lesion. Given these significant changes, a tissue diagnosis is warranted.

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**Figure 2. Case 1.** Axial T2-weighted image from the initial study (a) was compared with an image obtained 3 years later (b), and growth of the mass in the posterior left frontal lobe and insula is evident.
Neurosurgeon’s View

Question: How Should This Patient Be Approached Surgically?—The rationale for surgical resection of low-grade glioma is based on confirming the diagnosis and attempting to improve survival. The Joint Section on Tumors of the American Association of Neurological Surgeons/Congress of Neurological Surgeons has provided practice guidelines, with the only firm recommendation being that biopsy is the standard of practice whether observation or further treatment is recommended. Open operation for surgical resection is an option. How extent of resection influences time to progression and overall survival is still debatable, and most of the data available are level of evidence class II or III. Berger and Rostomily (11) found that a greater extent of resection and smaller residual volume corresponded to a longer time to tumor progression and a lower rate of malignant transformation (class III level of evidence). In a recent comprehensive review of the literature, Keles et al (12) found that in four of five studies with more than 75 patients, where pediatric patients and those with pilocytic tumors were excluded, extent of resection had a significant impact on survival in multivariate analysis (class II level of evidence).

Our approach for this young patient would be regarded as “aggressive,” as we would recommend open operation with motor-speech mapping and use of intraoperative navigation to help maximize the extent of resection and yet not produce new lasting speech deficits. A key feature of the original MR imaging findings that favors a good extent of resection is the distinct margins of the mass on T2-weighted images. This appearance translates to a visibly distinct, gelatinous, gray tumor for oligodendroglialomas/oligoastrocytomas and a white, rubbery tumor for astrocytomas.

Preoperative evaluation would include determination of handedness and assessment of lateralization of speech by ascertaining a possible history of speech disturbance and by using magnetic source imaging or functional MR imaging (13). Currently, we have focused on magnetic source imaging to assist with a prediction of speech lateralization and have used intracarotid amytal testing (Wada test) for left-handed individuals. A recent evaluation of this technique at our own institution demonstrated correct lateralization of speech in 71% of right-handed individuals (14). In addition, the patient would be seen by our neuropsychologist, who would evaluate the patient and review the parameters of intraoperative testing so as to include naming of objects presented on a computer screen and counting forward from one to 30.

The standard surgical approach to this tumor would be through a large left frontoparietotemporal craniotomy done under local anesthesia with intravenously administered sedatives. The patient would be placed in the Mayfield pin fixation device and given a lidocaine-marcaine mixture, and the registration of imaging to physical space would be performed by using the Stealth system and T2-weighted images. A reverse question mark scalp incision would be marked out after registration. After the craniotomy and exposure of the cortex, the motor cortex would be intraoperatively stimulated with a bipolar electrode with the smallest current necessary to evoke an observed motor response. Seizure activity can be terminated with iced saline irrigation or intravenous methohexital (Brevital). Numbered tickets are placed on the cortical surface, and the corresponding response for each site is recorded. The same threshold current is used to map the frontal operculum with the sites of speech arrest or altered phonation with stimulation. The entire lateral frontal surface is mapped with this technique, and sites of naming can be tested for tumors around the posterior superior temporal lobe or inferior parietal lobe. Subcortical mapping can also be done to test for speech association or descending motor pathways (15). Because most low-grade gliomas are a mixture of normal tissue infiltrated by glial cells, care must be taken around the sites of naming so as not to encroach within 1 cm of these sites to avoid permanent language disturbance. In the study by Skirboll et al (15), 83% of patients with low-grade gliomas that involved functional cortex had a new deficit immediately after surgery, but after 3 months only 16% had persistent problems. The right nondominant face motor cortex can be resected and result in a temporary facial weakness; however, resection of the same region on the dominant side almost always results in a permanent nonfluent dysphasia, even though this site may not produce speech arrest but rather altered phonation.

While intraoperatively evaluating the extent of resection, the surgeon must be aware of issues such as brain shift when imaging-guided systems are used, and that the closer one is to the surface, the greater the degree of brain shift. Reregistration with use of intraoperative ultrasound still has problems, and for low-grade gliomas, use of intraoperative MR imaging may be the best way to evaluate whether residual tissue remains (16). When we combined intraoperative mapping when
necessary and imaging guidance, the mean extent of resection was 96.7% (range, 80.8%–100%) in 21 patients with high-grade gliomas and four with low-grade gliomas (17). Not surprisingly, low-grade gliomas had only a 25% chance of gross total resection (15).

The patient underwent a left frontoparietotemporal craniotomy, cortical mapping, and subtotal resection conducted with an operating microscope. Pathologic analysis revealed a grade 2 oligodendroglioma with positive anterior and medial margins. MR imaging was performed on postoperative day 6 (Fig 3).

Figure 3. Case 1. (a, b) Axial T2-weighted MR images from a preoperative study (a) and from another study completed 6 days after surgery (b) reveal subtotal resection of the mass. (c, d) Gadolinium-enhanced axial T1-weighted MR images from the preoperative study (c) and another study performed 6 days after surgery (d) reveal a small amount of hemorrhage and new contrast enhancement within the operative bed.
Diagnostic Radiologist’s View

Question: What Is the Role of Postoperative CT and MR Imaging? Ideally, in What Time Frame Postoperatively Should These Studies Be Obtained? With the Images Available, What Are the Findings? Is the Finding of New Contrast Enhancement Postoperatively Unusual or Worrisome?—MR imaging, including studies performed without and with gadolinium-based contrast material, is the examination of choice in the postoperative period. This modality has greater sensitivity and specificity than computed tomography (CT) in determining residual disease in postoperative patients. Surgical complications can also be accurately defined with MR imaging. If possible, patients should be imaged within 24–48 hours of surgery, although benign gadolinium enhancement can be seen during and immediately after surgery (18). The characteristic of the enhancement pattern is more important than whether or not enhancement is present (19,20). Nodular or masslike areas of enhancement, leptomeningeal enhancement, and subependymal enhancement are suggestive of residual or recurrent tumor. The presence of hemorrhage in the operative field makes evaluation slightly more difficult. Nonenhanced and contrast-enhanced images must be carefully analyzed to differentiate enhancement caused by tumor from that due to postoperative hemorrhage. The finding of enhancement on postoperative images is not unusual and is secondary to the surgical procedure (21). In this case, the tumor did not enhance on preoperative images; thus, it would not be expected to demonstrate pathologic enhancement on the immediate postoperative images. Performing an initial MR imaging examination in the perioperative period allows comparison of all postoperative imaging studies to a baseline study.

Neuro-oncologist’s View

Question: What Is the Role of Chemotherapy in This Setting?—Presently, the role of chemotherapy compared with that of radiation therapy in the setting of a low-grade oligodendroglioma is unclear. Although the results from the only randomized study in which chemotherapy was used with radiation therapy to treat low-grade glioma were negative (22), there are more recent clinical data that indicated that low-grade oligodendroglioma responded to chemotherapy (23–27). These recent data showing benefit of chemotherapy included small studies that were limited in patient numbers and did not provide a comparison to radiation therapy. To date, information about durability of response is often limited. Even though chemotherapy should not be considered standard care in this setting, it does remain a viable option to the patient when discussing treatment (28).

Radiation Oncologist’s View

One of the controversies in the management of patients with low-grade glioma is in the timing of radiation therapy. Retrospective reviews of patients treated in the 1970s and 1980s demonstrated improved survival for patients treated with combined surgery and irradiation, particularly those with subtotally resected tumors. These results may reflect the limitations of surgery and surveillance imaging during that time as much as the efficacy of radiation therapy (29). In more recent series, the benefit of surgery and immediate radiation therapy is less obvious, and in some contemporary series, patients treated with the combined approach appear to do no better than those who underwent surgery with deferred radiation therapy. In our own experience (30), in univariate analysis, we found that postoperative radiation therapy was associated with worse survival than was observation after surgery. Our practice, however, was to select patients for postoperative radiation therapy on the basis of adverse prognostic factors, whereas patients with more favorable tumors (and a better prognosis) were observed. Once these prognostic factors were taken into account in a multivariate analysis, the timing of radiation therapy was not correlated with survival. Results of the European Organization for Research and Treatment of Cancer (EORTC) randomized trial of immediate versus deferred radiation therapy confirmed that the timing of irradiation (immediate vs delayed) did not influence overall survival for these patients but did confer improved progression-free survival (31). A key point here is that observation usually means “irradiation later” not “irradiation never.” Several multivariable prognostic models (32–35) have been reported and can be helpful in selecting patients for early versus deferred radiation therapy. For patients with adverse prognostic factors (larger or bilateral tumors, pure astrocytoma histologic type, older age, large residual tumor, impaired performance status), early progression after surgery alone is usually the rule and early use of radiation therapy can certainly be justified. For this 43-year-old patient with minimal symptoms,
a smaller tumor of pure oligodendrogial histologic type, and a generous tumor resection, observation would certainly be a reasonable option. After thorough discussion with a neuro-oncologist and radiation oncologist, the patient elected to proceed with observation. In a follow-up visit 3 months after subtotal resection of the grade 2 oligodendroglioma, the patient had no complaints and findings from the neurologic examination were unchanged. MR imaging was performed (Fig 4).

**Figure 4.** Case 1.  (a, b) Gadolinium-enhanced axial T1-weighted MR images from a 6-day postoperative study (a) and a study performed 3 months later (b) reveal resolution of the contrast enhancement in the surgical bed over time.  (c) Gadolinium-enhanced axial, axial T2-weighted, and coronal T1-weighted MR images obtained 3 months postoperatively show increased T1 and T2 extraaxial signal abnormality overlying the left frontal and parietal lobes.
Diagnostic Radiologist’s View

Question: What Is Your Interpretation of These Images?—The lesion is associated with a mild degree of mass effect on the underlying hemisphere. Involution of enhancement in the operative bed helps confirm that this enhancement was secondary to the surgery. The current MR images demonstrate interval development of a subacute-chronic subdural hematoma over the left frontal and parietal lobes. The subdural hematoma was evacuated through frontal and parietal burr holes. The patient’s postoperative course was uncomplicated, and she continued follow-up on a biannual basis. She returned 27 months after her subtotal resection for follow-up and had no new complaints. Her right-sided “spells” were stable. Neurologic examination revealed slight worsening of her right facial weakness and mild weakness of her finger extensors on the right. MR imaging was performed (Fig 5).

Diagnosis Radiologist’s View

Question: What Is Your Interpretation of These Images? Any Radiologic Evidence for a Dedifferentiation to a Higher Grade Tumor?—Obviously, there is tumor progression in this patient. The mass has substantially increased in size. Although the size of the mass has changed, there has been no change in T1 and T2 signal characteristics nor has there been a change in enhancement patterns. Tumor signal change and changes in enhancement patterns can be suggestive of tumor dedifferentiation (2,36).

Neurosurgeon’s View

Question: What Is the Role of Further Surgery in This Patient?—The patient has not undergone any therapy other than surgical resection, and she returns with clinical and radiologic features that suggest recurrence. Her clinical symptoms suggest infiltration of the primary motor cortex for the face and hand, two areas that we could not venture into surgically without causing permanent speech or motor deficits. On follow-up images, the tumor is smaller than on the original preoperative images, and I don’t think that more than 75% of the existing tumor volume could be removed at reoperation. Apart from recurrence, the other issue possibly represents malignant transformation. There is no enhancement on current images, but if there were concern about progression of tumor grade at recurrence (>70% of cases), a limited biopsy directed by means of preoperative MR spectroscopy could be done and its results may influence the recommendations for treatment. We have considerable experience now with correlating results of MR spectroscopy with pathologic characteristics, and we believe that the technique is most useful for evaluating the effects of prior therapy and directing biopsies in patients with nonenhancing tumors (37). In our most recent study by Mc-Knight et al, in which a choline/N-acetylaspartate index of greater than 2.5 compared with normal was used, biopsy samples containing tumor could be distinguished from normal, edematous, or gliotic tissue with a 90% sensitivity and 86% specificity (38).

Neuro-oncologist’s View

Question: What about the Other Treatment Options Available for This Patient Such as Further Observation, Radiation Therapy, Chemotherapy, or Radiation Therapy and Chemotherapy?—Given the worsening of neurologic signs and evidence of radiologic progression, the patient should strongly consider definitive therapy for this tumor. Further watchful waiting will likely lead to further neurologic deterioration. It is more common that with definitive therapy such as irradiation, a patient’s symptoms typically stabilize rather than improve. Therefore, it would be prudent to consider such a therapy in a patient with an actively growing tumor causing neurologic deficits while function is still good. One might even give stronger consideration toward therapy given the location of the tumor and the function of the underlying brain surrounding it when discussing therapeutic options with the patient (eg, a patient with a right frontopolar lesion might better be able to tolerate watchful waiting than a patient with a left frontal tumor...
Radiation therapy alone should be considered strongly. After thorough discussion with a neuro-oncologist, neurosurgeon, and radiation oncologist, the patient elected to proceed with radiation therapy.

**Radiation Oncologist’s View**

**Question:** What Are Some of the Technical Aspects of the Radiation Therapy for This Patient?—Some of the reservations about the
use of radiation treatments for patients with low-grade gliomas revolve around the potential for late neurocognitive side effects in a group of patients with often relatively indolent tumors and longer life expectancy. The neurocognitive toxicity of radiation therapy, at least with conventional fractionation schemes, is related to both dose and volume (39). In the past, radiation treatments were often delivered with whole-brain fields or large partial-brain fields and simple (minimal shaping, parallel opposed pair) beam arrangements. As a consequence, large volumes of uninvolved brain were irradiated, and patients experienced substantial neurocognitive side effects (memory, cognition) years later. With improved imaging, three-dimensional treatment planning computers, and sophisticated beam-shaping devices (multileaf collimators), it is now possible to precisely target and irradiate partial volumes within the brain. By restricting the volume of high-dose radiation to the T2-weighted MR imaging–delineated tumor volume through the use of multiple, overlapping, conformally shaped fields, the potential neurocognitive side effects are minimized (40). One very interesting area is the use of MR spectroscopy to identify areas of metabolic abnormality as a means to more precisely delineate tumor extent (41). If techniques such as these let us conform radiation beams even more tightly, neurocognitive side effects will be lessened still. The other issue is required dose, and we fortunately have two randomized trials to guide us in this regard. Both the EORTC and North Central Cancer Treatment Group (NCCTG) randomized trials failed to demonstrate a survival advantage to the use of higher (59.4–64.5-Gy) over lower (45–54-Gy) radiation doses. In fact, worse side effects (increased necrosis in the NCCTG trial, worse quality of life indexes in the EORTC trial) suggested the higher doses were detrimental (32,42,43). For this patient, I would recommend using a three-dimensional conformal radiation therapy technique, using T2-weighted MR imaging-CT fusion to delineate the tumor volume with a 1.5–2.0-cm margin, and delivering a total dose of 50.4–54 Gy in fractions of 1.8 Gy per day.

The patient was treated with three-dimensional conformal radiation therapy to a total dose of 54 Gy in 30 fractions. At completion of the radiation therapy, the patient noted decreased frequency of her spells, and at examination she was found to have improvement of her right facial weakness and resolution of the weakness of her finger extensors on the right.

Case 2

A 60-year-old woman with stage IIIb non-small cell lung cancer completed combined radiation therapy and chemotherapy. Six months later, she experienced an episode of upper extremity weakness that resolved 30 minutes later. She had no current complaints at a detailed neurologic examination, which revealed no focal deficits. MR imaging of the brain was performed (Fig 6) and demonstrated two separate regions with peripherally enhancing lesions that have newly developed since a previous MR imaging study of the head performed 8 months earlier.

Diagnostic Radiologist’s View

Question: What Is the Differential Diagnosis? Is a Tissue Diagnosis Needed?—The MR imaging characteristics of these lesions and their multifocal nature are highly suggestive of a metastatic process. Their low signal intensity on T2-weighted images and intermediate signal intensity on T1-weighted images could be secondary to hemorrhage or calcification. Although an infectious process could also manifest as multiple lesions, the signal-intensity characteristics of these lesions and the patient’s clinical history favor a diagnosis of metastatic disease (44–46). Further work-up, including imaging, revealed no other evidence of systemic disease.

Neurosurgeon’s View

Question: What Is the Role of Resection in This Patient?—The patient is presumed to have multiple brain metastases from lung cancer 6 months after original diagnosis and treatment of her primary tumor. The question is whether to resect one or both lesions and to follow surgery with some form of irradiation or to use radiosurgery instead of open operation (47).

At our institution, we offer open operation to patients with more than one metastasis only for salvage treatment when the primary tumor is clearly controlled. In some centers, multiple craniotomies performed with image guidance are offered to patients (48–50). We also screen patients for multiple metastases with triple-dose contrast-enhanced, thin-section MR imaging.
For this patient, I would not recommend either open operation or biopsy. Further imaging of the right parietal occipital lesion with MR spectroscopy or positron emission tomography would help define the nature of the lesions.

Another question is whether surgery alone provides sufficient local control. Bindal et al (48) reported the results of surgery alone in 62 patients
with metastases compared with those of radiosurgery in 31 patients. In the surgical group, 8.1% suffered local recurrence; 21.0%, distant recurrence; and 4.8%, both local and distant recurrence. Patchell et al (51), in a phase III randomized study of surgery alone versus surgery plus whole-brain irradiation for single brain metastases, found that 46% of patients treated with surgical resection alone had local recurrence in a median follow-up time of 43 weeks. We believe that surgery alone does not provide adequate local or CNS control in patients with multiple brain metastases.

**Radiation Oncologist’s View**

**Question: How Should This Patient Be Further Managed, with Whole-Brain Radiation Therapy, Radiosurgery with or without Whole-Brain Radiation Therapy, or Symptomatic Care? What Are Some of the Technical Aspects of the Radiosurgery for This Patient?**—This 60-year-old patient has three separate brain lesions seen on MR images 6 months after combined modality therapy for a stage IIIb non-small-cell lung cancer. Radiation therapy definitely has a role to play here, and the main question is how aggressive to be. In patients such as this one, it is usually a question of achieving intracranial control until the patient dies of other systemic disease. For patients with active systemic disease, a poor Karnofsky performance score, or multiple brain metastases, whole-brain radiation therapy alone may be the most pragmatic choice for palliation (52). For those patients with more favorable prognostic factors (no other sites of active systemic disease, one to three brain metastases, younger age, good function), symptomatic intracranial failure as the first site of disease progression may be a problem. In this instance, a more aggressive approach with either surgical resection or stereotactic radiosurgery of the metastases may be warranted. Certainly, the recently reported results of the Radiation Therapy Oncology Group (RTOG) randomized trial of whole-brain irradiation versus whole-brain radiation therapy plus radiosurgery boost suggest there may be subsets of patients who benefit from this approach. These findings are in keeping with those from other randomized trials and reported institutional series (53,54). There is some debate whether whole-brain irradiation must be added to surgical resection or radiosurgery. My personal preference is to recommend whole-brain radiation therapy, again from the point of view of improving intracranial control and preserving function, not from a desire to improve survival (51,55). From the technical aspect, if radiosurgery were chosen as part of the treatment, I think that gamma knife or LINAC-based radiosurgery are both equally good options. Most patients will be treated with a dose of 15–20 Gy prescribed to the edge of the contrast-enhancing volume seen on planning CT and MR images (56). With regard to whole-brain radiation therapy, I would usually recommend a dose of 30–40 Gy in 10–20 fractions. In the RTOG randomized trial, a whole-brain radiation dose of 37.5 Gy in 15 fractions was prescribed. My personal approach in this patient would be to treat her lesions with whole-brain irradiation alone and consider radiosurgery for salvage if there were isolated intracranial progression down the road.

After thorough discussion with a neuro-oncologist, neurosurgeon, and radiation oncologist, the patient elected to proceed with gamma knife radiosurgery (20 Gy to the tumor margin at the 50% isodose line) followed by whole-brain radiation therapy (3,750 cGy in 15 fractions).

Four months later, the patient developed progressive disease in the chest. Palliative chemotherapy was initiated, but her disease progressed after one cycle. She enrolled in a hospice and died 1 month later (9 months after gamma knife radiosurgery) of systemic disease.

**Case 3**

A 57-year-old previously healthy man presented with new onset of left-handed clumsiness and left-sided drooling. A detailed neurologic examination revealed left-hand incoordination, left-sided apraxia, and ataxia. MR imaging of the brain was performed (Fig 7) and revealed a large mass in the right frontoparietal region.

**Diagnostic Radiologist’s View**

**Question: What Is the Differential Diagnosis? Is a Tissue Diagnosis Needed?**—Differential diagnostic considerations would include a primary glial neoplasm or less likely an intracranial abscess (57–59). The prominent anterior, solid portion of the mass strongly favors a neoplasm. Diffusion-weighted imaging might have been helpful as a diagnostic tool in this case. A tissue diagnosis is warranted. Although the imaging appearance suggests a neoplasm, the tumor grade or cell type cannot be inferred from the images.
Figure 7. Case 3. (a, b) Nonenhanced axial T2-weighted images (a at lower level than b) and (c, d) gadolinium-enhanced axial T1-weighted images (c at lower level than d) demonstrate a mass in the right posterior frontal and parietal lobes with a mild amount of surrounding edema and moderate local mass effect. The heterogeneous mass is composed of a peripherally enhancing, posterior multiloculated cyst and a solid, poorly enhancing anterior component.
Neurosurgeon’s View

Question: How Should This Patient Be Managed, with Further Imaging Studies, Biopsy, or Resection?—First of all, given the variation in imaging features of the anterior and posterior components of the tumor, I would wonder about a so-called collision tumor. I would also recommend chest radiography and abdominal ultrasound to rule out a metastasis (posteriorly) abutting a glioma (anteriorly). Given that more than 80% of enhancing lesions in patients in this age group are malignant (grade III or IV), I do not think use of MR spectroscopy would improve tissue targeting for biopsy. However, results of MR spectroscopy and perfusion blood volume mapping may allow another tumor process to be excluded (45).

As for whether a biopsy should be performed or the tumor should be debulked, given the mass effect and necrotic, solid tumor tissue component posteriorly, I think craniotomy is preferred. There is some debate in the literature whether there is any advantage to open craniotomy versus biopsy for patients older than 60 years, but again mostly class III, single-institution data support one or the other viewpoint. The bulk of the literature on high-grade gliomas indicates that survival is improved by increasing the extent of resection from biopsy to subtotal to gross total resection. In summary, the absence of evidence of benefit is not evidence of absence of benefit, and some patients live longer, if not better, after debulking surgery.

If one assumes that the imaged lesion is a single entity, it appears to span the sensory motor cortex. Because the multiloculated component appears to be behind the motor cortex, I would recommend removing that component for diagnosis and decompression. The operation would be done with the patient asleep, with the use of imaging guidance and intraoperative motor mapping with electromyographic recording of motor responses (60).

The patient underwent stereotactic craniotomy and debulking of the enhancing cystic mass. During the procedure, cystic fluid and multiple loculations were encountered. Pathologic analysis revealed a glioblastoma multiforme. Gram stain and results of bacterial, anaerobic, and fungal cultures were all negative. MR imaging was performed on postoperative day 14 (Fig 8).

Neuro-oncologist’s View

Question: What Is the Role of Systemic Agents in This Patient?—Presently, it is unclear if there are effective systemic therapies for glioblastoma multiforme, whether the systemic agents are neoadjuvant, adjuvant, or given concomitantly with radiation therapy. Typically, systemic agents used in this setting have been chemotherapeutic. Most phase III studies of systemic agents used to treat newly diagnosed glioblastoma multiforme have yielded negative results (61–65); however, some information has been gained from these studies: (a) no systemic agent has provided evidence for a clinically significant radiosensitization, (b) approximately 10%–15% of patients benefit when systemic chemotherapy is used in the adjuvant setting (61,66), and (c) multiagent chemotherapy has no benefit over single-agent chemotherapy in treatment of high-grade gliomas (67).

Data are maturing about other potentially useful systemic agents in the treatment of glioblastoma multiforme. A recent phase II open label study described the use of temozolomide daily during radiation therapy at doses of 75 mg/m2 followed by adjuvant temozolomide doses at 200 mg/m2 per day for 5 days followed by 23 days off in repeating cycles. This single institution study of 60 patients reported a median survival of 16 months (68). The approach is presently being validated in a phase III study. Although these results provide some encouragement, they fall dramatically short of effective therapy. Therefore, clinical trial researchers are investigating many novel approaches for the treatment of this difficult disease. Given the advances in molecular biology, many novel targeted therapies for glioblastoma are being evaluated that target specific receptors, signal transduction pathways, angiogenesis, and other molecular events thought to be important in the pathogenesis or progression of glioblastoma multiforme (69). Use of many of these agents—either concomitantly with radiation therapy or adjuvantly or both—are being evaluated in patients with newly diagnosed glioblastoma.

Radiation Oncologist’s View

Question: What Is the Role of Radiation Therapy in This Patient? What Are Some of the Technical Aspects of Radiation Therapy for This Patient?—There is no doubt that adjuvant radiation therapy following surgery for high-grade glioma improves overall survival compared with surgery alone (61,70). That being said, the improvement is modest, on the order of 6–12 months for most patients, with few (<10%) long-term survivors. A dose response for high-grade gliomas has been demonstrated, with a maximum benefit achieved with radiation dose schedules of 50–60 Gy delivered over 5–6 weeks (71). The pattern of recurrence of these tumors, which is...
almost always within the original tumor volume, has led to many attempts at dose intensification with radiation therapy. Altered fractionation schemes to either shorten overall treatment times (72), escalate dose (73), or both (64) have failed to demonstrate an advantage over conventional radiation dose schedules. Likewise, dose escalation through focal irradiation techniques such as brachytherapy (74), three-dimensional conformal radiation therapy (75), proton beam irradiation (76), and radiosurgery has failed to improve survival. The biggest advance in radiation therapy in the past decade has been through the efforts of the RTOG to generate a robust historical database of patients with high-grade gliomas treated in prospective trials. Recursive partitioning analysis of this database has identified discrete prognostic subgroups of patients with median survivals of 6–18 months (77). I believe that we have probably reached a plateau in what conventional radiation therapy can offer to these patients and that improved results will require radiation therapy combined with other agents for better results. That being said, I would treat patients by using three-dimensional conformal techniques to irradiate the residual contrast-enhancing tumor volume (ie, gross tumor volume) with a 2–3-cm margin (clinical target volume) with a dose of 60 Gy in 30 fractions. I don’t typically add an additional margin to treat the edema (T2-weighted MR imaging) volume because the clinical target volume in this case often becomes prohibitively large and I’m concerned about potential toxicity. Failure patterns from use of three-dimensional conformal techniques and smaller treatment margins such as this have not demonstrated an increased rate of out-of-field failures (75,78).

In this case, the tumor appearance was somewhat atypical, and it is possible that the T2 changes anterior to the resected component might have represented tumor rather than just edema. In this case, I would include the T2 changes (as well as the resection cavity) with a margin as the gross tumor volume. I do review the T2-weighted MR images carefully, and, in patients whose tumors are clearly bilateral, extending into the corpus callosum or along white matter tracks, I tend to use more generous volumes (79). For patients with adverse prognostic factors (glioblastoma, older age, poor performance status), I tend to use shorter, hypofractionated fractionation schemes (30–40 Gy in 10–15 fractions) (80).

**Figure 8. Case 3.** Gadolinium-enhanced axial T1-weighted MR image obtained preoperatively (a), compared with a gadolinium-enhanced axial T1-weighted MR image obtained 14 days after surgery (b), reveals subtotal resection of the mass. The cystic component has been excised, and there has been little, if any, change in the anterior solid component.
After thorough discussion with a neuro-oncologist and radiation oncologist, the patient elected to proceed with radiation therapy alone. The patient was treated with three-dimensional conformal radiation therapy and received a total dose of 60 Gy in 30 fractions. After completing the radiation therapy, he enrolled in a prospective phase II trial of postirradiation ZD-1839, a selective epidermal growth factor receptor, tyrosine kinase inhibitor. Ten weeks later, he developed focal seizures, and at examination he was found to have a facial droop and left-sided weakness. MR imaging revealed local progression of the tumor, and he enrolled in a hospice. He died 4 weeks later (6 months after diagnosis).

Case 4
A 36-year-old woman presented with new onset of decreased visual acuity in her left eye and a 1-year history of floaters in the left eye. Her local physician diagnosed left optic neuritis and multiple sclerosis. Three years later, she noted progressive loss of visual acuity on the left side. Examination revealed a slightly pale fundus in the left eye, and vision on the left was 20/100. MR imaging of the head was performed (Fig 9).

Diagnostic Radiologist’s View

Question: What Is the Differential Diagnosis? Is a Tissue Diagnosis Needed?—Differential diagnostic considerations for a mass of the optic nerve within the orbit would include optic nerve glioma or optic nerve meningioma. Granulomatous disease, specifically sarcoidosis, could also manifest with these imaging findings. The circumferential, homogeneously enhancing appearance of the lesion with a thin residual segment of optic nerve centrally strongly suggests a meningioma.

Neurosurgeon’s View

Question: What Is the Role of Surgery in This Setting?—The clinical and imaging features are most consistent with those of an optic nerve sheath meningioma. Although the appropriate fat-suppressed imaging was performed, I cannot be certain about the posterior extent of the tumor. This characteristic is a key in the decision-making process for the management of these tumors: Extension posteriorly beyond the intracranial side of the optic canal excludes the chance of surgical cure. The only way to perform surgery in such a case would be to excise the optic nerve and sheath, resulting in total blindness. This approach is reserved for patients with no useful vision (<20/400) and no evidence of intracranial extension. The surgical approach in these rare cases is complex, with surgery lasting an average of 8–10 hours with a combined neurosurgical-ophthalmologic team.

The patient is young with still reasonable vision, so I would try to preserve the nerve and vision. I don’t believe there is any role for decompression of the optic canal or fenestration of the optic nerve sheath. Attempts to “remove” the subdural tumor mass are ill advised and if ever practiced, would result in blindness. I believe the best treatment is fractionated radiation therapy (82,83).

The real question is whether any tissue diagnosis is required before radiation treatment could begin, and at my center it would not be. We would recommend fractionated external beam radiation therapy and use of three-dimensional planning techniques, for which there are documented results of improved visual acuity after treatment. We would caution the patient against stereotactic or intensity-modulated methods, which may be associated with higher radiation doses to the optic apparatus and increased risk of toxicity.

Radiation Oncologist’s View

Question: What Is the Role of Radiation Therapy in This Patient? What Are Some of the Technical Aspects of Radiation Therapy for This Patient?—The patient would appear to have either a low-grade glioma or meningioma of the optic nerve. Although surgical resection would likely be curative for this patient, there would be no chance of preserving visual function with this approach. Moderate dose (45–50-Gy) irradiation has been associated with good long-term tumor control (84) and is just at or below the threshold for optic nerve damage (85). I advise patients that radiation therapy is more likely to preserve existing function and is less predictable in the recovery of lost visual function (84). The technical aspects of radiation delivery relate to the proximity of surrounding critical struc-
structures: lenses, right optic nerve, left retina, optic chiasm, brain stem, pituitary gland, and brain parenchyma. Beam trajectories must be chosen carefully to avoid entering or exiting the eyes, and a coronal beam arrangement can be useful in this regard (86). Fractionated, stereotactic radiation therapy techniques may provide some advantages (depending on the collimation system used). Meticulous, conventional three-dimensional conformal techniques, coupled with accurate immobilization and tumor volume delineation (MR imaging–CT fusion), can also be used to deliver 50.4 Gy in 28 fractions to the involved optic nerve.

Figure 9. Case 4. (a, b) Axial T1-weighted images obtained without (a) and with (b) gadolinium enhancement and fat saturation and (c, d) coronal MR images of the head and orbits obtained with gadolinium enhancement and fat saturation. The images show a circumferential soft-tissue mass that encases the left optic nerve and extends from the orbital apex to the middle aspect of the intracranial segment of the left optic nerve. A thin segment of the optic nerve can still be seen centrally within the mass.
After thorough discussion with a neuro-ophthalmologist and radiation oncologist, the patient elected to proceed with radiation therapy alone. The patient was treated with three-dimensional conformal radiation therapy for a total dose of 50.4 Gy in 28 fractions. She returned for follow-up 2 years later with improvement in her visual acuity. Follow-up MR imaging of the head (Fig 10) was compared with the baseline study, revealing stable findings with no change in the lesion involving the left optic nerve. Visual testing revealed improvement in the left eye, from 20/100 before radiation therapy to 20/20 2 years after radiation therapy.

References


