Brain Tumors: Prognosis and Treatment

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The human brain is a vital, complex organ, and a brain cancer diagnosis significantly affects patients and caregivers. Health care workers should learn to recognize complications of primary brain cancer and understand problems related to symptom management and quality of life. The complexity of the brain's anatomy and function make it difficult to manage symptoms and determine the best treatment. This article reviews normal brain function, brain tumor detection, symptom management, and therapeutic options for primary brain cancer.

After completing this article, the reader should be able to:

- Explain epidemiology and risk factors of primary brain tumors.
- Discuss normal brain anatomy, physiology, and histology.
- Distinguish among types of brain lesions and explain the brain cancer grading system.
- Describe the clinical presentation of symptoms and the diagnosis of brain cancer.
- Compare brain cancer treatment options.
- Summarize new and innovative research approaches to treatment.

In 2016, it is projected that nearly 78,000 new cases of primary central nervous system (CNS) tumors will be diagnosed in the United States.1 Such cases include malignant and benign tumors within the brain, spinal cord, pituitary and pineal glands, and the nasal cavity, as well as brain lymphoma and leukemia. Brain tumors rarely spread to other parts of the body but are locally invasive, causing significant problems with neurological function.2 Most brain tumors are associated with poor prognoses and can affect the quality of life for patients and their families. Because the complexity of symptoms associated with brain lesions can affect communication with or care for these patients, health care workers must understand normal brain functions and how brain lesions affect these functions.

Epidemiology

According to the Central Brain Tumor Registry of the United States, the incidence rate of primary malignant and nonmalignant brain and CNS tumors for 2008 to 2012 was 21.97 cases per 100,000 people.4 The risk of developing primary brain cancer is low; brain tumors account for 1.4% of all malignancies.5 A person's chance of receiving a diagnosis of primary malignant CNS cancer is estimated to be only 0.6% over a lifetime, excluding lymphomas, leukemias, olfactory tumors, and pituitary or pineal gland tumors.6,7

Brain tumors can occur at any age; however, CNS cancers are diagnosed most frequently in patients aged 55 to 64 years.7 The location of the tumor and type of cell influence when brain cancer occurs. For example, gliomas are more prevalent in adults, and medulloblastomas occur more often in pediatric patients. Sex and ethnicity also influence the likelihood of a brain cancer diagnosis. For example, women are more likely to develop meningiomas, but men have higher risk of developing...
tumors of neuroepithelial tissue. Incidence rates are higher among whites than among blacks. However, blacks have a higher chance of developing a meningioma or a pituitary tumor.

Although primary brain tumors are relatively uncommon, brain metastases can develop in up to 40% of cancer patients. Brain metastases most often occur in the cerebral hemispheres and appear as a single lesion (40%-45% of the time) or multiple metastases.

**Etiology**

Research on primary brain cancer has yet to determine the cause. Occupational and environmental exposures, medical conditions, lifestyle and dietary factors, and genetic factors might increase the risk of developing a brain tumor. Environmental toxins from industries such as oil refining, rubber manufacturing, and drug manufacturing have been linked to brain cancer. Chemical exposures to pesticides, herbicides, and fertilizers can lead to a higher incidence rate than normal for a population. There also is support for the role of vinyl chloride exposure in brain cancer development, specifically gliomas. Vinyl chloride is a petrochemical primarily used to make plastics.

Brain cancer also has been linked to exposure to ionizing radiation. Such exposure includes children and infants who received low doses of radiation (1000 cGy-2000 cGy) to treat tinea capitis (ringworm) or skin hemangiomas and patients receiving treatment for leukemia, lymphoma, and head and neck tumors. One study found that children younger than 5 years who were exposed to ionizing radiation had the highest risk of being diagnosed with malignant glioma. Exposure to nuclear bomb fallout and nuclear power plants also have been linked to radiation-induced brain cancer. Medical causes associated with brain cancer include drugs and viral infections. Although some reports have linked use of cell phones, nitrates, and hair dyes to brain cancer, insufficient clinical evidence exists in human subjects to support these behaviors or substances as known risk factors.

Some inherited gene mutations are known to contribute to the development of certain types of cancer. Genetic syndromes are associated with less than 5% of the etiology of brain tumors. Genetic disorders associated with brain cancer include:

- Von Recklinghausen disease, an autosomal dominant disorder linked to neurofibromin 1 and 2 (NF1 and NF2) genes.
- NF1 and NF2 linked to nerve sheath tumors, gliomas, and meningiomas.
- Li-Fraumeni syndrome linked to gliomas, medulloblastoma, nerve sheath tumors, and meningiomas.
- Turcot syndrome linked to medulloblastoma.
- Von Hippel-Lindau syndrome linked to hemangioblastoma.

Some research indicates a higher incidence among those who have a close relative diagnosed with a glioma. The chance that a relative of a brain cancer patient will be diagnosed with brain cancer is twice as high compared with a patient who has no relatives with a history of primary brain cancer.

Common occurrence of a mutant epidermal growth factor receptor (EGFR) is found in glioblastoma multiforme (GBM) tumors. The amplification, or the increase in the number of copies, of the gene EGFR is found in up to 50% of GBMs. This identification of gene amplification and mutation in GBMs has been linked to GBMs’ high resistance to radiation therapy and chemotherapy.

**Prognostic Indicators and Tumor Grading**

Length of survival following brain cancer diagnosis for U.S. patients varies according to patient age, tumor histology and behavior, and the patient’s performance status. The 5-year relative survival rate in the United States of individuals who have primary malignant brain and other CNS tumors is approximately 34%; the 5-year relative survival rate for people who have benign brain tumors is 92%. Factors such as age, tumor grade, and neurologic signs and symptoms affect a patient’s prognosis.

In general, younger patients have better prognoses as long as their brains have developed fully; the brain generally completes development around age 4 years. Treatment options for patients younger than 4 years can be limited by sensitivity to radiation. Radiation-induced adverse effects include decreased IQ scores and impaired mental functions. Adults who received radiation therapy as children have increased risk of emotional problems such as anxiety and depression, which can affect quality of life.
The Karnofsky Performance Status is a standardized numerical rating scale that measures the neurological and functional status of the patient. A patient is assigned a numerical value from 0 to 100 depending on ability to function in typical daily activities. A high score (≥ 80) means that the patient is able to perform activities of daily living. Patients who are unable to work but can care for themselves score in the 50 to 70 range. A low Karnofsky score (≤ 40) indicates a patient is disabled or extremely ill. This system helps to:

- Determine the patient’s prognosis.
- Monitor changes in a patient’s ability to function.
- Determine eligibility for clinical trials.

Brain lesions are categorized by the type of cell or tissue from which the tumor cells originate, the location of the lesion, and the grade of the tumor. Brain lesions are divided into benign or malignant classifications. Benign brain lesions are noncancerous, grow slowly, and have defined borders that do not spread to other parts of the brain. Generally, it is easier to surgically remove benign tumors than it is to remove malignant lesions because of the defined borders around benign tumors. Although benign lesions are usually slow to grow, they can cause life-threatening complications for patients by pressing on nearby brain tissue.

Malignant tumors grow faster and are more invasive than benign tumors. With brain tumors, both classifications are significant, however. Brain tumors rarely spread to other areas of the body, but nearby critical structures that become involved in the tumor volume cannot regenerate, which often leads to necrosis and permanent damage, affecting patient prognosis.

Brain lesions also are distinguished between primary and secondary (metastatic) lesions. Primary brain lesions originate in the brain and rarely metastasize to organs outside the CNS but often are locally invasive and cause significant morbidity. Primary brain cancers are less common than metastatic lesions.

Tumor grade is the primary factor involved with prognosis and staging of brain cancer. The brain tumor grading system comprises 4 grades and provides information on tumor aggressiveness (see Table 1). Most cancer staging systems are based on tumor location, size, lymph node involvement, and metastasis; however, for brain cancer staging, physicians rely on prognostic indicators that include type of tumor and grade, tumor size and location, and patient health and function level. Low-grade tumors (I and II) more closely resemble the tissue from which they originated and grow slowly. High-grade tumors (III and IV) are poorly differentiated, meaning they have abnormal-looking cells. As a patient’s disease progresses, the tumor grade will transition from a lower grade to a higher grade. A higher grade indicates a highly aggressive tumor and an associated poor prognosis.

Most patients have a recurrence of brain cancer following surgery for high-grade malignancies. Of these, 80% recur within 2 cm of the original tumor. Primary brain lesions occasionally invade cerebrospinal spaces, forming diffuse nodules. Called drop metastases, these lesions occur most often from GBM tumors. The secondary lesions can cause spinal cord compression and related pain or complications.

### Anatomy and Physiology

The brain is part of the CNS and provides communication for many important body functions. The brain has right and left hemispheres and 2 cerebellar hemispheres. The responses processed in the brain include involuntary and voluntary actions. The brain’s involuntary responses play an important role in maintaining homeostasis, which is crucial for survival. Homeostasis is a relative constancy of the body’s internal environment, including blood pressure, temperature, and pH. The brain is divided into 4 major parts: brainstem, cerebellum, diencephalon, and cerebrum (see Box 1). Four lobes comprise the cerebrum and control different functions (see Figure 1):
Brain Tumors: Prognosis and Treatment

- Frontal – problem solving, judgment, motor function.
- Occipital – vision.
- Parietal – sensation, handwriting, body position.
- Temporal – memory and hearing.

Symptoms of patients with brain cancer often correlate with tumor location, aiding in diagnosis.³

Protective Anatomy

The skull protects the brain, along with membranes, or meninges, and cerebrospinal fluid (CSF).⁴,⁵ The spinal cord passes through the foramen magnum, the largest opening at the base of the skull. Meninges are the inner protective lining consisting of 3 thin layers made up of continuous connective tissue (see Figure 2).

Box 1

Brain Anatomy⁷,⁸

Brainstem
- Located in the inferior portion of the brain in front of the cerebellum.
- Divided into the medulla oblongata, pons, and midbrain.
- Performs sensory and motor functions, along with autonomic functions, such as body temperature and respiration.
- Made up of a network of nerve fibers.

Cerebellum
- Located at the posterior base of the brain.
- Divided into cerebellum hemispheres and central vermis.
- Functions include skilled movement, balance, and posture.
- Made up of gray matter in the outer cortex; white matter primarily in the interior.

Diencephalon
- Located in the center of the brain, between the cerebrum and the mesencephalon (midbrain).
- Divided into the thalamus, hypothalamus, optic chiasma, and pineal gland.
- Involved in pain/pleasure responses, alertness, homeostasis, sleep cycle regulation, stress response, and complex reflexes.
- Right and left optic nerves enter the brain at the optic chiasma.

Cerebrum
- Largest portion of the brain in the uppermost portion of the skull.
- Divided into right and left hemispheres by the longitudinal fissure; each hemisphere is further divided into lobes.
- Involved in judgment, problem solving, memory, hearing, and vision (depending on the lobe).
- Bundled nerve tracts connect the hemispheres and gray matter.

Figure 1. Major structures and subsections of the brain. Image: iStock.
Some types of brain cancer occur most often in adults and some are found more often in children. Brain lesions traditionally have been classified based primarily on histology. In recent decades, researchers have learned much more about the genetics involved in tumorigenesis. In May 2016, the World Health Organization recommended a restructuring of brain tumor classification based on molecular information. This system likely will be refined and serve as the basis for molecular parameters in brain cancer classification, altering how lesion types are grouped.

Gliomas occur in children and adults. They are differentiated into several groups, including astrocytomas, ependymomas, oligodendrogliomas, and mixed gliomas. GBMs account for 15.1% of all primary brain tumors and 46.1% of primary malignant brain tumors, making gliomas the most common malignant brain lesion. These lesions originate in the glial supportive tissue.

The CSF provides a cushion of clear fluid around the brain and spinal cord. This fluid is formed in the choroid plexuses within the brain’s 4 ventricles, or cavities. The CSF then flows into the subarachnoid space, around the brain, and within the cavities and canals. It is essential that equal amounts of CSF be produced and reabsorbed at the same rate to maintain intracranial pressure.

**Blood Supply and the Blood-Brain Barrier**

The brain receives blood from the internal carotid arteries and vertebral arteries that travel through the circle of Willis. The blood contains oxygen, nutrients, and glucose, which is the primary source of energy for brain cells. No lymphatic channels are within the brain, which is a contributing factor to the low rate of metastatic spread from brain malignancies.

The blood-brain barrier, made of tiny impermeable capillaries in the brain, limits the passage of potentially damaging substances into the brain and controls the balance of electrolytes, glucose, and proteins in the brain. The barrier is located between the vascular system and the brain and is a highly selective diffusion barrier. It protects the brain from toxins and other compounds circulating in the blood but also makes it difficult for therapeutic molecules from the blood to enter the brain for cancer treatment. Substances must be lipid soluble to cross the blood-brain barrier. Water-soluble substances need a carrier molecule to cross the barrier through an active transport.

**Types of Brain Lesions**

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**Childhood Tumors**

Astrocytomas are divided into a variety of localized and diffuse neoplasms. These tumors originate from small, star-shaped cells called astrocytes located throughout the brain. Localized astrocytomas include grade I pilocytic astrocytoma. These slow-growing tumors usually occur in children and young adults. Pilocytic astrocytoma usually is found in the cerebellum, optic nerves and pathways, and hypothalamus.
Malignant anaplastic astrocytomas and GBMs make up 50% of all astrocytomas. GBMs are associated with poor prognosis; these lesions grow and spread aggressively. Only 2.2% of patients with GBMs survive 3 years.

Embryonal tumors affect children and tend to be aggressive and malignant. These tumors are classified as grade IV. The most common type of embryonal tumor is medulloblastoma. Medulloblastomas are found in the cerebellum, which controls coordination and posture.

Cranioopharyngiomas typically are benign. These rare tumors develop in the pituitary gland region near the hypothalamus. The hypothalamus maintains important body functions, such as temperature, hunger, and thirst. These vital functions might be affected or damaged if the tumor affects the hypothalamus. These lesions are more common in children and adolescents than in adults younger than 50 years.

Germ cell tumors originate from developing sex cells, or germ cells. Germinomas are the most common type of germ cell tumor in the brain. Germinomas also can develop in the ovaries, testicles, chest, and abdomen and most often are found in children.

Pineal tumors develop in the pineal gland, a small organ in the center of the brain responsible for producing melatonin, a hormone that regulates the sleep-wake cycle. Types of pineal tumors include pineocytoma (slow growing) and pineoblastoma (fast growing). The tumors are rare, but occur more often in children and adolescents or young adults than in older people.

**Adult Tumors**

Oligodendrogliomas are found in the frontal and temporal lobes, typically in young to middle-aged adults. The tumor typically is removed surgically. Adjuvant radiation therapy and chemotherapy also are used; the tumors respond well to chemotherapy.

Meningiomas account for 36.4% of primary brain tumors. Tumors found in the meninges are made of a large and diverse group of neoplasms. The most common primary type of meningeal tumor is the meningioma. Meningiomas can appear anywhere within the brain. Meningeal tumors are more common in women than in men and can grow quickly.

Diffuse astrocytomas are aggressive and are found along white matter tracts deep within the brain. Diffuse astrocytic neoplasms are divided into 3 categories: astrocytoma (grade II), anaplastic astrocytoma (grade III), and GBM (grade IV).

Pituitary adenomas are benign lesions located in the pituitary gland. The lesions can cause the pituitary gland to overproduce a variety of hormones, leading to symptoms such as fatigue, weight gain or loss, and menstrual irregularities. Pituitary adenomas are divided by size into macroadenomas (>1 cm) and microadenomas (<1 cm).

Schwannomas are encapsulated nerve sheath lesions that originate from Schwann cells. Schwannomas present as slow-growing benign lesions with no signs or symptoms for several years. Schwannomas typically occur in adults aged 20 to 50 years. Types of schwannomas include vestibular schwannomas and acoustic neuromas.

**Clinical Presentation and Diagnosis**

Detecting brain tumors as early as possible can lead to prompt treatment and increased survival rates. No screening tests are available to help identify brain tumors before symptoms appear. Classic signs and symptoms usually are the first indication of a brain tumor, although some are detected incidentally in diagnostic images.

The presentation of symptoms depends on several factors, such as type of tumor, location and extent of disease, patient age, and health history. Brain functions are

<table>
<thead>
<tr>
<th>Common Symptoms of Brain Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>A headache often is the initial symptom of a brain tumor.</td>
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<tr>
<td>Headaches are worse in the morning because of cerebral spinal fluid drainage upon rising.</td>
</tr>
<tr>
<td>Seizures are common and are caused by irritation of central nervous system tissue.</td>
</tr>
<tr>
<td>Decreased motor functions can include problems with balance and gait.</td>
</tr>
<tr>
<td>Large tumors can cause multiple symptoms because of pressure in the brain from the mass.</td>
</tr>
<tr>
<td>Examples of limited brain function include:</td>
</tr>
<tr>
<td>• Aphasia.</td>
</tr>
<tr>
<td>• Changes in cognitive function.</td>
</tr>
<tr>
<td>• Hallucinations.</td>
</tr>
<tr>
<td>• Mental and personality changes.</td>
</tr>
<tr>
<td>• Short-term memory loss.</td>
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<tr>
<td>• Vision changes.</td>
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</tbody>
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blood tests, electroencephalogram, and angiogram can help determine effects of a brain lesion.

A neurological workup includes several tests to determine the patient’s mental state, cognitive function, motor skills, and sensory function. Blood tests measure hormone levels and might detect genetic or chemical markers of brain cancer. Some brain lesions, such as pituitary tumors, affect hormone levels and can produce chemicals that are absorbed by the circulatory system.

An electroencephalogram records brain waves to detect abnormal changes, such as indications of a seizure. An angiogram, also known as an arteriogram, displays blood vessels and blood flow under image guidance and demonstrates the relationship between the tumor and surrounding blood vessels. The patient is injected with a contrast agent to observe blood flow to the brain. This information tells the surgeon which blood vessels supply the tumor and whether the tumor is attached to major blood vessels. Embolization or interventional angiography also might

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**Table 2**

**Signs and Symptoms of Primary Brain Tumors**

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glioblastoma multiforme</td>
<td>Nausea, vomiting, ataxia, increased intracranial pressure, abducens and oculomotor nerve defects</td>
</tr>
<tr>
<td>Anaplastic astrocytoma</td>
<td></td>
</tr>
<tr>
<td>Brainstem</td>
<td></td>
</tr>
<tr>
<td>Meningioma (B, M)</td>
<td>Localized headache, seizure</td>
</tr>
<tr>
<td>Astrocytoma (B, M)</td>
<td>Headache, seizure, unilateral weakness, mental changes, focal presentation related to tumor location</td>
</tr>
<tr>
<td>Cerebral</td>
<td>Headache, seizure, unilateral weakness, mental changes</td>
</tr>
<tr>
<td>Cerebellar</td>
<td>Occipital headache, increased intracranial pressure, abducens and oculomotor nerve defects, coordination deficits</td>
</tr>
<tr>
<td>Optic nerve</td>
<td>Ocular changes</td>
</tr>
<tr>
<td>Pituitary (B, M)</td>
<td>Vertex headache, ocular changes, ocular and endocrine abnormalities</td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>Morning headaches, nausea, vomiting, coordination deficits, increased intracranial pressure, abducens and oculomotor nerve defects</td>
</tr>
<tr>
<td>Ependymoma (B, M)</td>
<td></td>
</tr>
<tr>
<td>Hemangioma, arteriovenous malformation (B, M)</td>
<td>Migraines, focal presentation related to tumor location</td>
</tr>
<tr>
<td>Oligodendroglioma (B, M)</td>
<td>Insidious headaches, mental changes, focal presentation related to tumor location</td>
</tr>
<tr>
<td>Pinealoma (B, M) germinoma</td>
<td>Endocrine changes, ocular changes, increased intracranial pressure</td>
</tr>
<tr>
<td>Craniopharyngioma</td>
<td>Heads, mental changes, hemiplegia, seizure, vomiting, cranial nerve defects</td>
</tr>
</tbody>
</table>

Abbreviations: B, benign; M, malignant.

be performed to block blood supply to the tumor, causing tumor shrinkage before surgery.\textsuperscript{25}

Diagnostic imaging can help diagnose and grade brain tumors. Typical imaging modalities for brain cancer include computed tomography (CT), magnetic resonance (MR) imaging, and positron emission tomography. Brain lesions can appear on images as a calcification. Nearby structures might be displaced or eroded by the lesion. CT scanning can help physicians distinguish a tumor from normal brain tissue, as well as CSF, blood, and edema.\textsuperscript{2} Iodine-based contrast can highlight tumor extension, size, and growth pattern. The brain lesion is displayed as a contrast-enhanced volume on a brain CT image.

MR has several advantages over CT in diagnosing brain lesions (see Figure 3). MR images can display lesions smaller than 1 cm. In addition, MR does not expose the patient to ionizing radiation, and iodinated contrast is not necessary for detection of brain masses.\textsuperscript{2} Contrast enhancement is achieved through the use of gadolinium, which helps differentiate between edema and a tumor, and detects surface seeding.\textsuperscript{2}

Positron emission tomography scans are useful in determining differences between necrosis and malignancy.\textsuperscript{2} Malignant tumors are associated with high metabolism. These malignant areas are highlighted on the scan through the uptake of radionuclides, typically fludeoxyglucose F 18.\textsuperscript{2}

Biopsy of the tumor can provide more information for diagnosis and determining a treatment approach. Open biopsy is performed during a craniotomy when the tumor is exposed, whereas a stereotactic biopsy uses image guidance to locate the tumor. A stereotactic biopsy assists with studying the tumor and its borders before surgery changes the tumor volume.\textsuperscript{2} In some cases,

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{brain_tumor_image.png}
\caption{Magnetic resonance image with contrast of a brain lesion. Images courtesy of Duke University Hospital.}
\end{figure}
can experience mood disorders, such as depression and anxiety. Studies have shown that depression plays a key role in predicting QOL and survival in some patients with primary brain cancer. One study found that only 60% of patients who are depressed receive antidepressant medications; most are undertreated.

Symptom management is essential in maintaining QOL for patients. Physical symptoms are detected easily and can be treated. For example, doctors might place a cerebral shunt under the skin and outside the cranium to relieve symptoms caused by spinal pressure. The shunt drains excess cerebrospinal fluid from the brain and moves it to another part of the body. Intracranial pressure often causes headaches, nausea, and vomiting.

Corticosteroids help reduce swelling, improve neurologic function, reduce the risk of radiation-induced edema, and increase appetite. However, the medications can cause a patient to gain weight, have difficulty sleeping, and experience changes in mood. Steroid dosages must be tapered to reduce adverse effects of discontinuing the medication suddenly because the human body produces natural steroids, and when the body detects an abundance of steroids, it stops producing natural steroid hormones. Physicians might prescribe antiseizure medication for patients with a history of seizures related to a brain tumor and for patients at risk of having a seizure.

Neurological changes observed in patients with brain cancer can impose several challenges for caregivers and hospital staff. Counseling offers tips and guidelines to help patients and caregivers manage behavioral changes. Educating caregivers on how to recognize changes in behavior and when to intervene is helpful. Counseling family members also helps them balance their QOL as they care for loved ones.

Treatment Options

Brain tumors often are invasive and aggressive, affecting nearby healthy brain tissue and critical structures. Treatment is necessary for benign and malignant tumors to reduce effects on healthy tissue, manage symptoms, and improve prognosis. Earlier diagnosis and aggressive treatment improve the chance of survival; however, the nature and size of brain tumors can cause complications that
must be considered when determining treatment options. Healthy tissue invaded by brain lesions cannot regenerate, and some brain functions can be diminished permanently. Tumors also can attach firmly to nearby healthy tissue, including arteries and cranial nerves.

Treatment of a brain lesion can be limited because of critical structures close to or surrounding the lesion. When critical structures such as the brainstem and optic nerve are involved, access to the brain lesion is limited, and healthy tissues might not tolerate radiation doses needed to eradicate the lesion. The presence of any residual tumor cells following treatment increases the risk of tumor recurrence in healthy brain tissue. Therefore, partial removal of a tumor does not increase patient survival. A multidisciplinary approach that includes surgery, chemotherapy, and radiation therapy often is used to treat primary brain cancer.

**Surgery**

The primary goal of surgery is to remove as many tumor cells as possible and obtain a histological diagnosis. Surgery should be performed for tumors that are symptomatic and offer a chance of complete resection. Preoperative evaluation is essential to provide the surgeon with information, such as tumor size and extent, and to obtain a baseline of associated symptoms. Tests involved in preoperative evaluation can include blood analysis, an angiogram, and neurological observation. Recent advancements significantly have improved the knowledge surgeons can gather preoperatively. These include introduction of microsurgery, ultrasonic aspiration, perioperative ultrasonography, and computer-assisted stereotactic neuronavigation.

The most common approach for treating brain cancer is surgical resection of the lesion through a craniotomy. A surgical craniotomy involves temporarily removing a bone flap from the skull, allowing the surgeon access to the brain. If a complete resection is not possible, then cytoreduction, also called debulking surgery, can be performed for large, accessible tumor volumes. Cytoreduction decreases the tumor size and aids in obtaining a pathological diagnosis, but it does not increase survival.

New approaches to surgery include enhancing minimally invasive techniques. Such techniques include approaching the tumor through the nasal cavity or skull base and retractorless surgery. Limiting factors, such as tumor location and extent, poor patient health, and risk of neurological damage, can contraindicate surgery. Risks associated with surgery include seizures and swelling. Radiation therapy and chemotherapy might be applied before, after, or both to enhance surgical effects. When surgery is limited or not an option, radiation therapy is a key method for treating brain cancer.

**Radiation Therapy**

Radiation therapy provides additional treatment options for patients with brain cancer, increasing survival time and improving their QOL. The primary goal of radiation therapy is to destroy tumor cells while sparing as much healthy tissue as possible. Radiation therapy usually follows surgery to treat residual disease and prevent recurrence. Radiation is indicated for malignant tumors that are incompletely excised, inaccessible, and associated with metastatic lesions from another primary site.

When prescribing a radiation dose and designing a treatment plan, the radiation oncologist must consider tumor type, grade, and pattern of spread. Radiation dose is limited to normal brain tissue tolerance to prevent radiation necrosis and adverse effects of radiation. Adverse effects of radiation to the brain include temporary hair loss for total doses between 20 Gy and 40 Gy, permanent hair loss at greater than 40 Gy, erythema, darkening of pigment, dry and moist desquamation, and edema. Up to 3 months after treatment the patient might experience delayed reactions to radiation therapy that include drowsiness, lethargy, difficulty speaking, decreased mental status, and worsening of symptoms that had been present at diagnosis. These adverse effects usually are temporary and resolve on their own.

Radiation necrosis can occur from 6 months to several years following treatment and is irreversible. Radiation-induced cataracts can occur because of proximity of radiation to the orbits but can be avoided through the proper use of eye shielding. Radiation therapy can result in local failure and disease recurrence. Hypoxia and poor immunological status of the patient can lead to local control failure. Use of radiosensitizers and hyperthermia (heat) can boost the effects of radiation therapy in brain cancer treatment.

Radiosensitizers can enhance the effects of radiation on tumor cells while sparing normal tissue. Tumor
cells tend to have a lower level of oxygen than do healthy cells, which makes cancer cells less sensitive to radiation. Radiosensitizers increase the oxygen level in tumor cells, improving the effectiveness of radiation therapy. Common radiosensitizers for brain cancer include motexafin gadolinium (Xcytrin), efaproxiral (Efaproxyn or RSR13), and bortezomib (Velcade), as well as thalidomide, teniposide, topotecan, paclitaxel, and cisplatin.\textsuperscript{10}

Radiation therapy for brain cancer can be delivered as external-beam radiation therapy (including tomotherapy), interstitial radiation therapy, and particle therapy. External-beam radiation therapy is the most common radiation therapy used to treat brain cancer.\textsuperscript{15} Radiation is the primary treatment for metastatic brain lesions, typically in the form of whole-brain irradiation delivered using lateral photon beams and a 2-cm margin and eye block (see \textbf{Figure 4}). This approach also is used in the treatment of meningeal disease because the meninges encompass the entire brain, from the optic nerve to the orbit, and cervical spinal cord. The first 2 cervical vertebrae might be included in the whole-brain treatment field. The typical dose for palliative whole-brain radiation ranges from 30 Gy to 37.5 Gy delivered in 10 to 15 fractions.\textsuperscript{2}

When it is not necessary to treat the entire brain, CT and MR scans help the radiation oncologist and treatment planning team accurately delineate tumor volume and nearby critical structures. With this information, the team generates a treatment plan with a smaller margin around the gross tumor volume, minimizing dose to nearby healthy tissue. It is important to include a margin around the gross tumor volume when the lesion is associated with edema because tumor cells can be present in the fluid.\textsuperscript{15} Typically, recommendations include a 1-cm to 3-cm margin beyond the gross tumor volume of the lesion.\textsuperscript{15}

The treatment approach might include a 3-D plan, an intensity-modulated radiation therapy plan, a volumetric modulated arc therapy plan, or an arc design (see \textbf{Figure 5}). These plans can have tight margins around the tumor volume and require image-guided localization before treatment delivery (see \textbf{Figure 6}). Conventional fractionation delivers radiation ranging from 1.8 Gy to 2 Gy once daily, for a total dose of 54 Gy to 60 Gy.\textsuperscript{11}

Stereotactic treatment uses radiation instead of surgical tools to treat a small lesion and might be recommended instead of surgery for tumors that are inaccessible via resection, tumors surrounding critical structures, or poor patient condition.\textsuperscript{7} Postoperative radiation therapy and
brain tumors that are surgically unresectable, but the implants do not play a primary role in brain cancer management. Interstitial implants use radioactive (iodine 125) seeds that are placed temporarily in tumors. The radiation dose decreases rapidly outside the implanted tumor volume, sparing nearby healthy tissue. This allows a higher dose to be delivered to the tumor. Brachytherapy to brain lesions can provide an alternative for children and adolescents, for whom late adverse effects are of special concern.

Particle therapy uses subatomic particles, which improves dose localization to the tumor volume and offers biological effects superior to effects from photons.

Chemotherapy
Chemotherapy involves administering anticancer drugs into the bloodstream to treat rapidly dividing cancer cells. Chemotherapy is administered orally, intravenously, directly, or by direct carotid perfusion. A challenge with using chemotherapy for brain cancer is identifying drugs that will cross the blood-brain barrier to reach tumor cells in the brain and minimize adverse effects to rapidly dividing normal healthy cells such as chemotherapy are used for the treatment of malignant tumors to eliminate any residual disease.

Brain stereotactic treatment administers a high dose of radiation to a well-defined tumor volume in 1 to 5 fractions. This is an option for isolated CNS tumors and solitary brain metastases. Stereotactic treatment delivery includes stereotactic localization techniques with a sharply collimated beam. Stereotactic irradiation can be delivered through a linear accelerator, CyberKnife, or Gamma Knife. Target volumes typically have a 1-mm margin or less and require involvement of both a radiation oncologist and neurosurgeon in developing a treatment plan. Precision and accuracy are crucial and are enhanced by appropriate immobilization and patient setup. Patients typically are immobilized with a head ring screwed into the patient’s skull or a tightly conforming thermoplastic mask (Aquaplast, Qfix). Acute complications from radiosurgery generally are minimal. Adverse effects might include numbness from the pin site, headache, seizures, nausea, vomiting, fatigue, and an increase in existing neurologic symptoms. Physicians might prescribe corticosteroids or antiseizure medication upon discharge. Late adverse effects include radiation necrosis, steroid dependency, and continued neurologic symptoms that originally presented.

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Other radiation therapy treatment options include brachytherapy and particle therapy. Interstitial implants for brachytherapy can be used for small tumors that are surgically unresectable, but the implants do not play a primary role in brain cancer management. Interstitial implants use radioactive (iodine 125) seeds that are placed temporarily in tumors. The radiation dose decreases rapidly outside the implanted tumor volume, sparing nearby healthy tissue. This allows a higher dose to be delivered to the tumor. Brachytherapy to brain lesions can provide an alternative for children and adolescents, for whom late adverse effects are of special concern. Particle therapy uses subatomic particles, which improves dose localization to the tumor volume and offers biological effects superior to effects from photons.

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hair follicles and bone marrow. Once a substance penetrates the blood-brain barrier, astrocytes can absorb and break down certain foreign substances, creating a second barrier to chemotherapy agents.

As of summer 2016, chemotherapy agents used for brain cancer include carmustine, procarbazine, vincristine, and lomustine. Temozolomide is a lipid-soluble alkylating agent that has shown promising results in the treatment of malignant gliomas. Although chemotherapy typically is not the primary form of treatment for brain cancer, use of chemotherapy is common for patients with high-grade lesions. When a brain tumor grows more than 1 mm to 2 mm, structural and functional damage can occur to the blood-brain barrier, causing easier permeability.

Research does not support the use of chemotherapy as the only treatment option for brain metastases. When planning chemotherapy, physicians must consider each patient individually, noting age, performance status, chemosensitivity of the tumor, pathology type, and extent of the disease.

Future advancements could include chemotherapy agents that enhance whole-brain radiation therapy (WBRT) and small molecule inhibitors that can permeate the blood-brain barrier easily. Other innovative techniques being investigated to address the challenge of the blood-brain barrier include placing the chemotherapy agent directly on the tumor site or directly in the CSF. This approach increases the drug concentration at the tumor site while reducing typical adverse effects of systemic chemotherapy.

**Targeted Therapy**

Immunotherapy, or biologic therapy, is a targeted therapy that stimulates the immune system to attack cancer cells. Targeted therapy is aimed at specific molecules in cells that contribute to cancer cell growth or progression. The immune system’s function in defending the body from bacterial or viral infections includes recognizing and fighting cancer cells. However, studies have found that cancer cells can hide from and escape the immune system. Immunotherapy agents aid the immune system by marking certain cell types so the immune system can recognize and kill cancer cells or by boosting the immune system in general so it is more effective in addressing cancer.

Several novel approaches in immunotherapy now support brain cancer treatment. Identification of more molecular markers has refined the diagnosis of many brain tumors into distinct histological types. This information is helping oncologists deliver substances only to malignant cells, sparing normal ones. Other therapies target proteins on cell surfaces that signal growth. Two common FDA-approved drugs used for targeted therapy are bevacizumab (Avastin) and everolimus (Afinitor). Avastin is a monoclonal antibody that prevents new blood cells from forming, preventing tumor growth. Afinitor prevents tumor growth by blocking the signaling pathway of a cell protein known as mechanistic target of rapamycin (mTOR). This protein promotes cell growth and division.

Much investigation has been done into alternative medications and combinations of medications to treat brain lesions, and one of the biggest hurdles remains the blood-brain barrier. Well-documented evidence supports the oncogenic activity in a number of cancers from abnormal tyrosine kinase, and the search for an inhibitor has been a focus of research for years. In 2002, the first tyrosine kinase inhibitor, imatinib, was approved as a treatment for cancer and still is the primary treatment for some cancers because it results in remission in many patients. Imatinib originally was developed to bind and control kinase activity instead of allowing binding to adenosine triphosphate (ATP).

In 2012, a study was conducted to determine the viable use of imatinib combined with hydroxyurea as a treatment for adults with low-grade gliomas (LGGs). Most often, LGGs affect children as well as young to middle-aged adults and often are mistakenly considered to be benign because they have a slow growth rate. It is common for LGGs to cause neurologic, cognitive, and personality issues in those with the disease because it can infiltrate extensively before it is diagnosed correctly. There is no clear directive for treatment of LGGs and surgical intervention has not proved to be curative.

The lack of options for adequate treatment has fostered much research into chemotherapeutic regimens, including the combination of imatinib and hydroxyurea, a ribonucleoside diphosphate reductase inhibitor. The combination was reviewed in a single institutional phase II study to evaluate whether improved survival rates were observed and if radiographic response was achieved. The
authors found that the combination was tolerated well, but results were negligible in the patients they evaluated.\textsuperscript{40}

Another study reviewed imatinib’s effect on medulloblastomas when combined with other medication-based treatments.\textsuperscript{39} Combining imatinib with a histone deacetylase inhibitor and a demethylating agent improved cell cytotoxic effects on medulloblastoma more than without imatinib. This finding supports the need for further research into their combined use in medulloblastoma treatment.\textsuperscript{39}

Since imatinib was approved in 2002, other medications in the same family have been released. Nilotinib, a second generation tyrosine kinase inhibitor, was approved and introduced to the medical community in 2010.\textsuperscript{38} Nilotinib provides a second-line treatment for those who cannot tolerate or have become resistant to imatinib. However, several patients who were treated previously with imatinib did not have a favorable response to nilotinib.\textsuperscript{39} Although nilotinib use has been encouraging for some cancers, when it comes to GBM little evidence suggests that it inhibits tumor growth or improves survival. The results of a study published in 2016 suggested potential adverse effects with the use of imatinib and nilotinib for GBM cases, and proper patient screening is necessary to ensure the disease is not accelerated.\textsuperscript{38}

In a 2015 study, Hatipoglu et al investigated the use of another inhibitor, sunitinib.\textsuperscript{41} The authors reviewed the effect sunitinib had on the microenvironment of malignant glioma lesions.\textsuperscript{41} They found that sunitinib causes endothelial cell death, specifically on tumor vessels, but the results can be increased by combining it with temozolomide. The study showed that sunitinib is not toxic to, nor does it affect cell growth of astrocytes or neuron survival. However, according to the study, sunitinib does provide a dose-dependent reduction in glioma cell viability by impairing cell growth and causing cell death in primary GBM tissue.\textsuperscript{41}

The use of sunitinib also has been investigated for its effectiveness in treating meningioma.\textsuperscript{42} A majority of patients are treated with surgery and radiation; however, in rare cases, patients develop recurrences and have no therapeutic options available. In these cases, positive results have been observed with the use of tyrosine kinase inhibitor-based treatments. Marosi et al demonstrated a 6-month progression-free rate of 42% in those who received a tyrosine kinase inhibitor treatment compared to a 30% rate for those not treated with a tyrosine kinase inhibitor.\textsuperscript{42}

The use of a tyrosine kinase inhibitor for brain lesions has exhibited positive and negative results, and the benefits of using these inhibitors are debatable. However, some evidence suggests positive results in rare and extreme cases with the use of tyrosine kinase inhibitor–based treatments. Considering that many malignant brain lesions carry a poor prognosis, the potential to provide some improvement to patients’ quality of life and survival is worth exploring.

**Future Direction of Treatment**

Surgery followed by radiation therapy and chemotherapy remains the standard approach in the treatment of brain cancer. However, it is important to investigate new techniques to continue to improve prognosis for patients who have brain cancer and to minimize potential neurocognitive effects of treatment. Many areas of active investigation are ongoing; they share the goal of improving the treatment of brain cancer.

**Radiation Therapy Advancements**

Linear accelerator–based radiosurgery typically targets a single intracranial tumor volume by placing the isocenter in the center of the volume.\textsuperscript{43} A separate isocenter is used for each targeted area in patients with multiple targets. When all the targets are treated in the same session, the setup is repeated continuously until all areas are treated, leading to a lengthy amount of time on the treatment table for the patient. A new concept involves a single isocenter radiosurgery for multiple intracranial targets (SIRMIT). The patient is treated with volumetric arc therapy that targets multiple lesions with a single isocenter. Challenges with this therapy concept include increased emphasis on setup accuracy and decreased plan quality for targets near the edge of the treatment area.\textsuperscript{43}

Rotational errors around the isocenter with SIRMIT can lead to a large displacement of the dose, compromising coverage to distal tumor volumes.\textsuperscript{44} It is crucial to minimize rotation in the SIRMIT technique through a 6-D correction as seen on image guidance or to use a frame-based system for immobilization. Previous radiosurgery studies have shown improved dosimetry when using smaller multileaf collimator widths, an advantage when treating smaller targets.\textsuperscript{44} The SIRMIT technique
could pose challenges when paired with a linear accelerator equipped with multileaf collimation of various leaf widths. Isocenter placement would then be crucial to ensure the best plan quality for all targets.

**Whole-Brain Radiation Therapy Controversies**

Clinicians continue discussing the role of radiation therapy for brain metastases. WBRT has remained the standard of care since the 1950s because of its ease of treatment delivery and palliative treatment effectiveness. Patients with favorable prognostic factors are beginning to live longer because of advancements in neurosurgery, imaging, medical oncology, and radiation oncology. Potential adverse effects of WBRT, such as a decline in neurocognitive function and QOL, must be considered when determining treatment options. Several prospective trials are exploring ways to mitigate the potential neurocognitive effects of WBRT through advances in pharmacology, radiation therapy treatment planning, or by omitting WBRT completely.

Radiation-induced inflammation and ischemia could be the reasons for adverse neurocognitive effects of WBRT. The inflammation and ischemia lead to excess glutamate, which is found in the hippocampus, and pathologic overstimulation of the N-methyl-D-aspartate receptor involved in memory and cognition. The Radiation Therapy Oncology Group (RTOG) 0614 investigated the effects of the drug memantine on reducing cognitive dysfunction. Memantine also is used for the treatment of vascular dementia. The small vessel disease seen with vascular dementia has similar characteristics to radiation-induced injury in the brain. Memantine acts as an N-methyl-D-aspartate receptor antagonist. The RTOG trial found that the use of memantine during and after WBRT resulted in better cognitive function over time with little to no toxicity. Many clinicians now prescribe memantine to patients receiving WBRT who are expected to live longer than 4 months.

RTOG 0933 investigated the relationship between WBRT with hippocampal avoidance and memory preservation. The reason for early cognitive decline during radiation therapy is the radiosensitivity of the hippocampus. In the RTOG trial, a radiation dose of 30 Gy was delivered in 10 fractions to a treatment field designed to reduce dose to the hippocampus. The mean radiation dose to the hippocampus was reduced by 80% while maintaining adequate coverage and dose homogeneity for the remaining whole brain. Gondi et al found a link between hippocampal avoidance WBRT and preservation of memory and QOL compared with standard WBRT.

A new approach to avoid WBRT altogether is being investigated. Yamamoto et al suggested that stereotactic radiosurgery without WBRT in patients has the same results when comparing patients with 5 to 10 brain metastases to patients who have 2 to 4 brain metastases. For patients with good performance status (Karnofsky scale), stereotactic radiosurgery might be an appropriate treatment option because it is minimally invasive and associated with fewer adverse effects than WBRT. Little evidence suggests that WBRT for brain metastases improves survival compared with supportive care alone. For patients with poor performance status, supportive care alone might be a suitable option.

**Emerging Treatment Options**

Recent breakthroughs could have exciting implications in how we treat brain cancers. A phase I clinical trial using a genetically engineered poliovirus (PVSRIPO) against recurrent GBM brain tumors is under way. Viruses designed to infect and kill cancer cells must safely target cancer cells, spread within the tumor, and avoid healthy cells. To remove the chance of poliovirus causing natural disease, researchers inserted a portion of the rhinovirus genetic code into the poliovirus genome. The ability of the PVSRIPO virus to grow and destroy cells depends on biochemical abnormalities found only in cancer cells.

To ensure the tumor receives the maximum amount of the virus, the PVSRIPO is infused directly into a patient’s tumor. Once the tumor absorbs the PVSRIPO, the infection spreads within the tumor and kills its cells. In addition to PVSRIPO tumor cell destruction, PVSRIPO can trigger a patient’s immune system to recognize the viral infection and fight the infected tumor. This combination shows promise in targeting recurrent GBM (see Box 3). Various nanomedicine strategies are being applied to enhance the therapeutic response of drug-resistant tumors. Such strategies include directly targeting cancer stem cells and noncancer stem cells for elimination. Some have suggested that cancer stem cells are the primary cause of current chemotherapy resistance and...
Box 3

Update on PVSRIPO

CBS “60 Minutes” aired an update for the PVSRIPO trial on May 15, 2016. Although this subject is controversial among providers, Duke University was awarded Breakthrough Therapy Designation by the U.S. Food and Drug Administration, which will expedite the development and review of this treatment approach. PVSRIPO gained this status because preliminary evidence showed the new approach has substantial improvement over available therapy; however, it is still too early to predict how this treatment will affect all patients.

What are your thoughts on this treatment?
Start a conversation in your Community at asrt.org/myasrt.

recurrence of GBM. The cancer stem cell hypothesis suggests that tumors are initiated from and maintained by a small fraction of malignant cells that have properties similar to stem cells. Stem cell–like properties cause resistance to cytotoxic therapies and allow cancerous stem cells to continue to change into rapidly multiplying differentiated tumor cells (noncancer stem cells). In GBM tumors, cancer stem cells tend to be more resistant to radiation therapy and chemotherapy than are noncancer stem cells. Cancer stem cells also possess increased abilities to repair DNA damage and to promote angiogenesis, or the development of new blood vessels. Therefore, cancer stem cells that survive after anticancer therapies can cause a tumor to recur.

Another strategy for improving cancer treatment is the use of nanotechnology to help deliver drugs across biological barriers, such as the blood-brain barrier. A series of biological barriers can hinder nanoparticles from reaching their targeted site inside the cell when administered systemically. Typically, nanoparticles must travel through the extracellular matrix, penetrate the tumor cell membranes, and be released into the cytoplasm. A nanotechnology-based delivery platform takes advantage of the blood vessels in tumors in which the endothelia are not intact because of rapid and defective angiogenesis.

When administered intravenously, nanoparticles passively extravasate into tumor tissue through the leaky vasculature. The nanoparticles accumulate in the tumor bed because of poor lymphatic drainage and release therapeutic agents near tumor cells. This process is known as the enhanced permeability and retention effect. In the case of brain tumors, the effect is unlikely to work because of a dense brain matrix impeding diffusion, the elevated interstitial fluid pressure, and the blood-brain barrier. To address this issue, researchers are investigating ways to attach nanoparticles to substances that can cross the blood-brain barrier.

Conclusion

Advancements in the treatment of brain cancer have improved prognosis, and some patients with brain tumors are living longer after a brain cancer diagnosis. When individuals are faced with the diagnosis of a brain lesion, they find that simple daily functions are impaired and that overall QOL can deteriorate quickly.

Brain cancer patients and their caregivers often face challenges managing multiple symptoms simultaneously, which can lead to secondary symptoms such as depression and anxiety. Radiation therapists must be prepared to provide emotional support and monitor their patients’ mental and physical well-being. It is essential for radiation therapists and other caregivers to recognize difficulties that patients and their family members might have coping with a brain cancer diagnosis and provide tools that help them maintain their QOL.

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Bollinger


Directed Reading

Brain Tumors: Prognosis and Treatment


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Brain Tumors: Prognosis and Treatment

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Read the preceding Directed Reading and choose the answer that is most correct based on the article.

1. The risk of developing a brain tumor is associated with exposure to:
   a. toxins from rubber manufacturing.
   b. pesticides and herbicides.
   c. radiation.

   a. 1 and 2
   b. 1 and 3
   c. 2 and 3
   d. 1, 2, and 3

2. Research has indicated that gene amplification occurs in up to 50% of:
   a. glioblastoma multiformes (GBMs).
   b. pituitary adenomas.
   c. germ cell tumors.
   d. meningiomas.

3. The 5-year relative survival rate in the United States of individuals who have primary malignant brain or other central nervous system tumors is approximately ______ %, and the 5-year relative survival rate for people who have a benign brain tumor is ______ %.
   a. 19; 36
   b. 34; 92
   c. 53; 77
   d. 61; 88

4. The Karnofsky Performance Status measures:
   a. the strength of epileptic seizures.
   b. short-term memory recall.
   c. the neurological and functional status of a patient.
   d. tumor size.

5. Eighty percent of high-grade brain malignancies recur within ______ cm of the original tumor.
   a. 5
   b. 3
   c. 2
   d. 1

continued on next page
6. The brainstem comprises the medulla oblongata, pons, and:
   a. basal ganglia.
   b. central vermis.
   c. hypothalamus.
   d. midbrain.

7. _____ account for 15.1% of all primary brain lesions and 46.1% of primary malignant brain tumors.
   a. Ependymomas
   b. GBMs
   c. Mixed gliomas
   d. Oligodendrogliomas

8. Advantages of magnetic resonance as a diagnostic tool for brain lesions include that it:
   1. can display lesions smaller than 1 cm.
   2. does not expose the patient to ionizing radiation.
   3. does not require the use of iodinated contrast.
   a. 1 and 2
   b. 1 and 3
   c. 2 and 3
   d. 1, 2, and 3

9. _____ decreases the tumor size and aids in obtaining a pathological diagnosis when complete resection is **not** possible and does **not** increase survival.
   a. Cytoreduction
   b. Minimizing surgery
   c. Microblasing surgery
   d. Craniotomy

10. Permanent hair loss occurs at total radiation doses to the brain **greater** than _____ Gy.
    a. 35
    b. 40
    c. 45
    d. 50

11. The recommended margin around gross tumor volume when the lesion is associated with edema is _____ cm to _____ cm.
    a. 0.5; 1
    b. 3; 5
    c. 1; 3
    d. 2; 2.5

12. Conventional (3-D and modulated radiation therapy) fractionation delivers radiation for a total dose of _____ Gy to _____ Gy.
    a. 16; 30
    b. 23; 35
    c. 31; 45
    d. 54; 60

13. _____ is a form of targeted therapy that stimulates the immune system to attack cancer cells.
    a. Chemotherapy
    b. Immunotherapy
    c. Microblasting surgery
    d. Whole-brain radiation therapy (WBRT)

14. RTOG 0933 investigated the relationship between:
    a. memantine and WBRT.
    b. WBRT and stereotactic radiosurgery.
    c. WBRT with hippocampal avoidance and memory preservation.
    d. image-guided radiation therapy and chemotherapy.