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## Low Grade Astrocytomas

Astrocytomas are tumors that are believed to arise from precursors of astrocytes – supportive cells of the brain named for their star-like shape. Astrocytomas are the most common of the primary brain tumors. The pathologist, using a microscope, grades these tumors on a scale of I to IV based on how quickly the cells are reproducing, as well as their potential to invade nearby tissue. Grade IV astrocytomas, also called glioblastoma, are the most aggressive of the astrocytomas. Glioblastoma cells reproduce rapidly. Grade III astrocytomas, also known as anaplastic astrocytomas, reproduce at an intermediate rate. Grades I and II astrocytomas are the slowest growing tumors, and are also called low-grade astrocytomas. This article reviews new developments in our understanding and treatment of low-grade astrocytomas.

Low-grade astrocytomas are relatively uncommon tumors when compared to their higher-grade counterparts; only about 1,500 are believed to occur in North America each year. Their cause is unknown, and current research indicates that the environment does not seem to play a role in their origin. However, families with neurofibromatosis, a genetic inherited disorder, are at increased risk of developing these tumors.

Low-grade astrocytomas can be further sub-grouped into three tumor types: pilocytic astrocytomas, pleomorphic xanthoastrocytomas, and diffuse astrocytomas. Diffuse astrocytomas are by far the most common.

Pilocytic astrocytomas are most often found in children. They have a tendency to arise in the cerebellum – the part of the brain that controls balance. Pilocytic astrocytomas have sharply defined boundaries. For this reason, they are often curable with surgery if located in an accessible part of the brain. Radiation or chemotherapy are generally used to treat inaccessible or partially removed tumors.

Pleomorphic xanthoastrocytomas, also referred to as “PXAs,” most commonly occur in children and tend to be superficially located in the brain. As with pilocytic astrocytomas, surgery is the primary treatment.

Diffuse astrocytoma typically arises in young adults, although they are also found in children and senior citizens. They may be found anywhere in the brain, but are most common in the cerebral hemispheres – the “thinking” part of the brain. As the name implies, the borders of a diffuse astrocytoma tend to grow into surrounding normal brain tissue. Seizures and headaches are very often the earliest signs of this tumor; weakness on one side of the body (hemiparesis) is also common. CT and MR scans show the presence of this tumor, which typically does not “enhance” or “light up” when an intravenous contrast dye is given.

Once a scan shows an abnormality suspected of being a low-grade astrocytoma, the next step is generally a consultation with a neurosurgeon or neuro-oncologist. The neurosurgeon may recommend a biopsy to confirm the diagnosis or surgery to remove the tumor. When tumors are located near vital brain areas, neurosurgeons may use sophisticated techniques including functional MRI and intraoperative surface mapping of brain function to help with tumor removal.

However, if this is a diffuse astrocytoma, the tumor usually has already grown tiny microscopic tentacles that spread into the surrounding brain tissue. Those tentacles cannot always be seen by the neurosurgeon. They also intermingle with brain cells that are performing their normal important functions. As a result, “complete” tumor removal may not be possible. The extent of surgery depends on the location of the tumor, the patient’s symptoms and personal preferences, and the neurosurgeon’s philosophy.

Once the diagnosis of diffuse low-grade astrocytoma is confirmed by tissue examination, the next issue is the type and timing of subsequent therapies. Options may include radiation, chemotherapy, or even careful observation.

The question often arises as to whether astrocytomas should be considered benign or malignant. The question of how “benign” and “malignant” should be defined in the brain – where tumor location may be as important as tumor aggressiveness – is hard to answer. Pilocytic astrocytomas are generally considered benign tumors. Brain tumor experts agree that while diffuse astrocytomas are usually slow growing, they should not be considered benign.

Often the first treatment consideration following diagnosis of a low-grade astrocytoma will be radiation. Radiation therapy can be used to reduce the size of the tumor, and may improve symptoms. Although the optimal timing and dose of radiation for this type of tumor is still being studied, several recent clinical trials improved our understanding of radiation’s role.

The timing of radiation for low-grade astrocytomas is a longstanding controversy. Some physicians believe radiation therapy should be used “early” – as part of the initial treatment plan. Others suggest “deferring” radiation (and therefore delaying any related side effects) until scans show tumor re-growth. A large randomized European trial recently examined the question of “early” versus “deferred” radiation therapy. Although early radiation slightly delayed the average time until the tumor started re-growing, the overall outcome of both the early and deferred groups were identical. It was also noted that about two-thirds of the people in the deferred group required radiation about five years after diagnosis. Thus, either early radiation or deferred radiation may both represent reasonable options in certain cases.

Results from two recent clinical trials focusing on low-grade gliomas helped clarify the optimal radiation dose and schedule. Neither study revealed an advantage for higher doses of radiation, and suggested that five to five and a half weeks of treatment is preferable to six or seven weeks.

In addition to concerns about the timing and dose of radiation for low-grade astrocytomas, physicians are also learning more about the effects of radiation therapy on a person’s ability to think. These “cognitive” side effects of treatment include poor short-term memory and a diminished ability to concentrate. Until the 1980s, there was a tendency to give radiation therapy to the whole brain; cognitive impairment among long-term survivors of whole-brain radiation therapy was common. Newer technologies make it possible for radiation oncologists to focus

the treatment on the tumor and a small margin around the tumor, thus minimizing radiation to the tumor-free parts of the brain. Two studies of people with low-grade astrocytomas treated with focal radiation therapy found a lack of cognitive effects in the first few years after treatment, providing reassurance that current radiation therapy procedures are well tolerated.

These studies also show that fatigue and depression are common in patients with low-grade astrocytomas whether or not they receive radiation. Thus, some symptoms commonly attributed to radiotherapy may be more appropriately blamed on the tumor itself.

A recent study demonstrated that so long as the tumor did not grow, cognitive function remained stable in the overwhelming majority of patients. However, the cognitive function tests used were designed to be quickly administered and are not good at detecting subtle changes. In summary, evidence suggests that radiation has become substantially safer, and that most patients do not suffer major problems as a consequence of radiation. Further studies are required to assess the long-term risk of more subtle impairment in concentration and memory.

Recent success in treating another type of low-grade glioma – oligodendroglioma – with chemotherapy has sparked renewed interest in the use of chemotherapy for low-grade diffuse astrocytomas. Additionally, many low-grade gliomas have some areas that resemble astrocytoma and other areas that resemble oligodendroglioma – such tumors are called oligoastrocytomas or mixed gliomas. Several small studies have shown that chemotherapy, either with PCV (a combination of the three medications procarbazine, CCNU, and vincristine) or the newer chemotherapy pill temozolomide (Temodar) may stop low-grade gliomas, including astrocytomas, from growing, and in some instances, may shrink the tumors. Recently, a large clinical trial opened in Europe and Canada to test how well temozolomide works compared to radiation. People with previously untreated low-grade gliomas that are growing or causing symptoms randomized to receive either temozolomide pills or radiation. When this trial is completed, we will be more knowledgeable about whether initial treatment with chemotherapy is a good alternative to radiation.

Because both radiation and chemotherapy are helpful in some circumstances, doctors are studying whether the combination of radiation and chemotherapy may be more effective than each treatment alone. A recent study randomized people with low-grade gliomas to radiation alone or immediately followed by PCV chemotherapy. This study found that people receiving the combination of radiation and PCV had a longer period of time until their tumor began growing than people who received radiation alone. However, the overall survival in both groups was identical, indicating that the PCV chemotherapy was as effective when delayed until the tumor started growing as when given immediately after radiation. The ambiguous results of this study are mitigated by the fact that many more doctors and patients are now utilizing temozolomide in lieu of PCV. In the related but much more aggressive brain tumor “glioblastoma,” the combination of radiation and temozolomide is markedly more effective than radiation alone.

Thus, although there are several reasonable initial strategies for management of low-grade astrocytomas, there is no single approach that can be recommended for all patients. Patients should discuss all options carefully with their medical team. More insights may come from further studies looking at whether a tumor’s chemical makeup helps to predict whether one type of treatment will be more effective than another. Such analyses are focusing on whether an individual low-grade glioma has lost pieces of chromosomes 1p and 19q (much more common in oligodendrogliomas than astrocytomas) a protein called MGMT that helps to repair damage

from chemotherapies like PCV and temozolomide, thereby potentially making the chemotherapy less effective.

When diffuse astrocytomas recur following treatment, they frequently come back as a biologically more aggressive tumor. People with these tumors are generally eligible for the full spectrum of clinical trials available to patients with high-grade gliomas. Those clinical trials are testing novel treatment approaches ranging from stimulation of the body's natural immune system and drugs which choke off the tumor's blood supply (a technique called anti-angiogenesis inhibition), to drugs that selectively target biochemical pathways revved up in tumor cells, but inactive in healthy cells (signal transduction inhibition). Thus, progress in the more common high-grade gliomas should eventually translate into a better outcome for patients with diffuse astrocytomas.

The American Brain Tumor Association's Care Line is here to help. Call one of our Care Consultants at 800-886-ABTA (2282).

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