CNS

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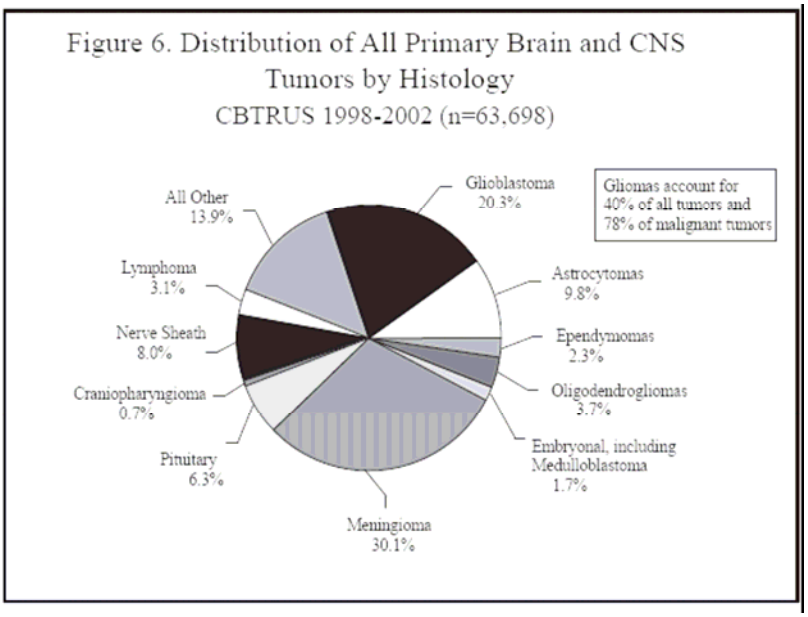
"Benign" vs. "Malignant' Brain Tumors

Brain tumors typically behave in a unique fashion compared to neoplasms occurring elsewhere in the body. In particular, they rarely spread to other parts of the body and typically produce symptoms due to localized growth within the brain. For this reason, neoplasms in the brain, even malignant tumors, are typically referred to as "tumors" as opposed to "brain cancer".

"Benign" brain tumors are those tumors that typically grow in a well-circumscribed fashion and do not invade surrounding brain tissue or other structures. Despite their name, "benign" brain tumors can still be life or function threatening, particularly when they occur at the base of skull where they can affect normal structures like the brainstem, eyes and cranial nerves and where treatment with surgery or radiation may be difficult. Typical benign brain tumors include: meningioma, acoustic neuroma, pituitary adenoma and craniopharyngioma.

"Malignant" brain tumors are those tumors with a propensity to grow quickly, invade normal brain and/or spread to other parts of the neuroaxis. Typical malignant brain tumors include glioblastoma and anaplastic astrocytoma. Low grade gliomas may be slow growing neoplasms but often recur despite conventional treatments and can exhibit malignant transformation over time. Other malignant brain tumors include primary CNS lymphoma and medulloblastoma. A breakdown in the distribution of adult CNS tumors is included below (source: Central Brain Tumor Registry; http://www.cbtrus.org)



Etiology/Risk Factors:

The cause of CNS tumors is unknown. Familial aggregations have been observed but most occur sporadically. Several inherited disorders such as neurofibromatosis and tuberous sclerosis are associated with a variety of CNS neoplasms. Chronic exposure to toxins found in the petrochemical industry and elsewhere may predispose to glioma. Cranial and spinal irradiation may predispose to meningioma, fibrosarcoma and glioma. Severe head injury may be a risk factor for meningioma and glioma. Chronic immunosuppression and Epstein Barr virus infection are associated with primary cerebral lymphoma.

Staging and prognostic factors:

Since there are no lymphatics in the brain and systemic metastasis is a rare event, staging of the "TNM" type is not customary for most CNS tumors. Tumors that have the potential to seed the subarachnoid space are notable exceptions. Medulloblastoma ependymoma, pineocytoma, germinoma and CNS lymphoma are "staged" prior to treatment. Staging includes CSF cytologic examination and imaging of the whole neuraxis. Malignant gliomas, the common brain cancers of adults, are not staged in the traditional sense but age at diagnosis, performance status after surgery and tumor histology are important prognostic factors. Independent of treatment, younger patients live longer than older ones, those with good function live longer than those with poor function, and patients with anaplastic gliomas live longer than those with glioblastoma multiforme.

Brain Tumor Symptoms

Headaches:

Headaches in patients with brain tumor can usually be controlled with simple oral analgesics (e.g. acetaminophen; acetaminophen with codeine). If headaches are due to raised intracranial pressure, steroids may be more effective than analgesics.

Cerebral Edema and hydrocephalus:

Increased intracranial pressure due to cerebral edema or hydrocephalus can result in cognitive impairment, focal deficits (sensory or motor) and headaches. Patients with hydrocephalus may require a temporary ventricular drain or a ventriculoperitoneal shunt. Steroids (usually dexamethasone) are used preoperatively, postoperatively and during the early phases of radiotherapy to control these symptoms. Since prolonged steroid use is associated with a number of significant medical problems (hyperglycemia, oral candidiasis muscle weakness, susceptibility to infections, change in metabolism of other drugs like phenytoin), steroids should be tapered and discontinued whenever possible or used in the lowest dose necessary to control CNS symptoms.

Seizures and neurologic deficits:

The commonly used anticonvulsants are phenytoin (Dilantin*), carbamazepine (Tegretol), primidone (Mysoline) and phenobarbitol. Anticonvulsants are given to all patients with tumor-related seizures. Many physicians caring for patients with

brain tumor use anticonvulsants prophylactically. In Ontario, patients with seizures that impair consciousness or motor control must be reported to the Ministry of Transportation and ordinarily cannot resume driving until the seizures have been controlled on medication for at least one year. Those with other severe neurologic deficits that might impair their ability to drive safely should also be reported to the Ministry of Transportation.

Fever:
Urinary tract infections and pneumonia are the commonly encountered infections in patients with primary brain tumor. There have been several reports of pneumocystitis carinii pneumonia in brain tumor patients receiving steroids chronically as well as patients receiving concurrent chemotherapy and radiation. Some authors recommend that steroid dependent patients be treated with prophylactic Septra. Gastrointestinal tract perforations with peritonitis and scalp or bone flap infections are uncommon, serious infections. Note, steroids will often mask the typical symptoms and signs of infection in these patients. Occasionally, fever in brain tumor patients is drug-related and caused by phenytoin, carbamazepine or procarbazine allergy.

Nausea/Vomiting:
Nausea and vomiting are most commonly the result of increased intracranial pressure due to tumor growth, cerebral edema, or hydrocephalous, and are best managed by treating the underlying cause (surgery, radiotherapy, corticosteriods, ventriculoperitoneal shunt, etc.). Nausea or other gastrointestinal symptoms may complicate corticosteroid therapy and can often be relieved by histamine-2 antagonists (ranitidine, etc.) or proton pump inhibitors (i.e. losec). Nausea and vomiting complicating cranial radiation can often be prevented or relieved by low dose corticosteroid therapy; intractable nausea/vomiting during radiotherapy may require ondansetron Zofran).

Pulmonary Embolism/Thrombophlebitis:
Pulmonary embolism and thrombophlebitis are common problems in brain tumor patients. Anticoagulation is not contraindicated in most primary brain tumor patients. Anticoagulation may be contraindicated in patients with hemorrhagic brain metastases, such as occur with malignant melanoma. Prophylactic anticoagulation is not recommended in patients with brain tumor. Patients with primary brain tumor and signs or symptoms of suspected pulmonary embolism and thrombophlebitis should be investigated promptly for these symptoms and treated as required.

Diagnostic Imaging
Enhanced computed tomography (CT) when it was introduced in the 1970's revolutionized the management of brain tumor patients and remains an excellent and widely available imaging modality for brain tumor. Gadolinium enhanced magnetic resonance imaging (MRI) was developed a decade later is now the preferred preoperative imaging modality for most primary brain tumors. MRI is

invaluable for assessing leptomeningeal spread by primary brain tumors such as medulloblastoma, pineocytoma and germ cell tumors. Enhanced and unenhanced T1 weighted, T2 weighted and FLAIR MRI images are helpful in assessing the tumor and associated edema. Positron Emission Tomography, Single Photon Emission Tomography and MRI Spectroscopy are newer imaging modalities that show promise in providing additional information regarding tumor metabolism and biology but are not yet standard imaging modalities.

Surgical Considerations

Surgery relieves symptoms, establishes a definitive diagnosis and guides subsequent treatment. For most primary brain tumors maximum feasible surgical resection is recommended. For non-invasive, “benign”, primary brain tumors complete surgical resection is potentially curative. These tumors may occur in the base of skull area where complete surgical excision is difficult, in these cases subtotal resection or biopsy only with adjuvant radiation is an option.

For patients with malignant brain tumors evidence that aggressive surgery prolongs survival for patients is lacking and generally speaking resections aim to remove as much tumor as possible without creating new neurologic symptoms/deficits. For some tumors in deep locations (i.e. thalamus) stereotactic biopsy is indicated as the tumor may be inaccessible to resection. In highly selected cases where the risk of surgery is judged too great, radiation or other treatment may proceed in the absence of a tissue diagnosis (e.g. brainstem glioma). At recurrence re-operation is recommended for selected patients, for example, younger patients with good performance status and those who have enjoyed a long period of tumor control following initial therapy. Surgical adjuncts to improve the efficacy and/or safety of surgical resection include stereotactic biopsy, intraoperative ultrasound, ISG wand (i.e. a three-dimensional "viewing" device), awake craniotomy with cortical mapping and stereotactic computed-assisted tumor resection.

Radiation

As mentioned, radiation may be recommended for patients with “benign”, non-invasive brain tumors if complete surgical resection is not possible. As some “benign” brain tumors may behave very indolently, the timing of radiotherapy with respect to surgery may be less critical and some patients may be observed following a subtotal resection with radiation reserved for evidence of tumor progression after surgery.

Radiotherapy is recommended for most patients with malignant tumors, especially those with good neurologic function after surgery as surgery alone is usually associated with early tumor recurrence. For malignant glioma and medulloblastoma the benefits of radiotherapy have been demonstrated conclusively in randomized trials, but for most other malignant CNS tumors conclusions are based on the results of single arm studies or retrospective analyses.

For “benign” tumors, radiation courses of 5-6 weeks of daily radiation (Monday-Friday) delivering between 45-54Gy over 25-30 fractions (treatments) are typically used. Radiation treatment planning involves fabrication of an immobilization shell (mask) and acquisition of a CT scan to provide the three-dimensional volumetric information that allows planning of treatment with multiple conformal (shaped to match tumor volume) radiation fields are used to treat the tumor volume while sparing organs at risk (uninvolved brain, optic chiasm and nerves, brainstem and spinal cord etc). Image guided and intensity modulated radiotherapy provide additional capabilities for highly focused radiation treatments particularly for those patients with base of skull tumors where high radiation doses and/or multiple organs at risk need to be considered.

For “malignant’ brain tumors, radiation doses are somewhat higher (50-60Gy) but are otherwise delivered in a similar fashion. The propensity of malignant brain tumors to invade normal brain requires that larger volumes of brain tissue be irradiated to insure coverage of areas of potential microscopic spread. For those patients with tumors that have a propensity for spread through the CSF (medulloblastoma, pineoblastoma, ependymoblastoma) or for those patients with demonstrated CSF spread, craniospinal irradiation to treat the whole CSF space may be necessary.

Chemotherapy

For malignant glioma, the nitrosoureas, procarbazine and other alkylating agents have been shown to have anti-tumor activity in phase II studies but most randomized trials have either failed to demonstrate that adjuvant chemotherapy significantly prolongs median survival or have shown only modest benefit. Metanalyses support the view that treatment of malignant glioma in adults using adjuvant nitrosourea based chemotherapy is associated with a small overall benefit (perhaps 5% absolute survival benefit at 2 years post treatment). More recently, a large randomized trial of radiation with concurrent followed by adjuvant temozolomide chemotherapy has demonstrated a survival benefit over adjuvant radiation alone in adults with glioblastoma. Another large randomized trial demonstrated a progression free survival advantage to the use of neoadjuvant PCV (procarbazine, CCNU, vincristine) chemotherapy in adults with anaplastic oligodendroglial tumors. At this time, adjuvant chemotherapy with radiation might be considered for patients with a malignant glioma (glioblastoma, anaplastic astrocytic or oligodendroglial tumors) who are younger (i.e. age< 65) and who have a better performance status (i.e. KPS >=70).

For patients with medulloblastoma (primarily children and young adults), randomized trials have shown a benefit to the addition of chemotherapy to craniospinal radiation. For patients with favorable risk disease (no spread to the craniospinal access and near complete surgical resection), chemotherapy may allow lower craniospinal radiation doses with a reduced chance of cognitive side effects. For those patients with more advanced medulloblastoma (residual tumor

or evidence of craniospinal spread) chemotherapy added to full dose craniospinal radiation has been shown to improve survival over craniospinal radiation alone. Cisplatin, CCNU and vincristine are active agents for the treatment of medulloblastoma. Etoposide and cyclophosphomide may be useful in the treatment of recurrent disease.

For the treatment of CNS lymphoma there is increasing evidence based on single arm studies that adjuvant treatment with methotrexate and cytosine arabinoside prolongs survival. Data from phase II studies suggest that adjuvant cisplatin-based chemotherapy regimens may be helpful for some patients with primary intracranial germ cell tumors.

For many other types of brain cancer, chemotherapy is either ineffective or untested. Treatment decisions must be individualized and in some instances supportive care (i.e. palliative) is the wisest course of action. For example, supportive care may be the most appropriate recommendation for elderly patients with glioblastoma and those with poor neurologic function.

Side Effects of Treatment

Common early side effects from radiation include: hair loss and mild sunburn of the scalp; tiredness; change in taste or mild dry mouth; irritation of the ear canal or fluid in the middle ear. Less common early side effects from radiation include: headaches; worsening of seizures or other symptoms from the tumor; nausea or vomitingFollowing radiation energy level and other side effects will generally improve over 4-6 weeks after radiation however temporary return of tiredness and/or worsening of symptoms may occur 2-3 months after radiation. Hair re-growth occurs slowly (4-6 months) and may not be complete. Potential long term effects (6 months or more after radiation) include: effects on thinking or memory (severe impairment rare); changes in vision (rare); Stroke-like brain injury (rare); effects on pituitary (hormone) function (can be common if the pituitary is included in the radiation field); radiation related second brain tumor (very rare, less than 1 in 1000 patients). Nausea and vomiting regularly accompany chemotherapy; highly emetogenic chemotherapy (cisplatin, nitrosoureas) may require ondansetron or high-dose metoclopramide; moderately emetogenic agents (temozolomide) may be adequately treated with prochlorperazine (Stemetil) or dimenhydrinate (Gravol). Lowered blood counts (platelets or neutrophils) resulting in bleeding or infection may occur with chemotherapy. These side effects usually manifest between 2 and 6 weeks following administration of chemotherapy are usually reversible however may necessitate a dose reduction if they are severe. Long term side effects of chemotherapy may include hearing loss (for cisplatin based regimens) and rarely, risk of secondary leukemia (particularly for etoposide based regimens). Temozolomide, an oral based chemotherapy agent is the most common drug used for malignant glioma and has a generally favorable short and long term side effect profile.

Rehabilitation:

Physiotherapy, occupational therapy and speech therapy are helpful for selected patients, particularly for those patients who are expected to have a more indolent course or who are treated for cure where maximizing functional recovery will impact on long term quality of life.

Follow-Up

Patients are usually followed at 3-4 month intervals year 1-2, 6-12 monthly thereafter and may be more frequent for those receiving ongoing treatment. Follow-up usually includes a neurologic examination and imaging with CT or MRI. If tumor recurs, it usually does so in the original location in the brain. Thus, return or worsening of presenting symptoms may indicate tumor recurrence and early reassessment by the neuro-oncology service is recommended. Salvage treatments for tumor progression may include repeat surgery, re-irradiation, chemotherapy or combinations. Symptomatic/palliative care is indicated for individuals where salvage treatments are felt to be either too toxic or unlikely to help.